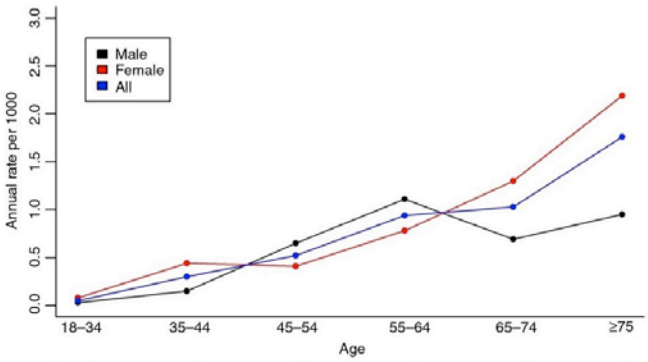
Le trombosi venose superficiali: patologia frequente, ma con punti ancora oscuri

Sabina Villalta

Bologna 6-7 febbraio 2020

Epidemiologia



Incidenza annuale **0.64%**
Concomitante TVP **24.6%**
EP sintomatica **4.7%**.

AGE (years)	18–34	35–44	45–54	55–64	65–74	≥75	Total
Men							
Cases	1	3	13	22	9	12	60
Rate/1000 (95% CI)	0.03 (0.00,0.08)	0.15 (0.00,0.32)	0.65 (0.30,1.00)	1.11 (0.65,1.58)	0.69 (0.24,1.14)	0.95 (0.41,1.48)	0.49 (0.36,0.61)
Women							
Cases	3	9	9	17	21	52	111
Rate/1000 (95% CI)	0.08 (0.00,0.17)	0.44 (0.15,0.73)	0.41 (0.14,0.67)	0.78 (0.41,1.15)	1.30 (0.74,1.85)	2.19 (1.59,2.78)	0.78 (0.63,0.92)
Total							
Cases	4	12	22	39	30	64	171
Rate/1000 (95% CI)	0.05 (0.00,0.10)	0.30 (0.13,0.46)	0.52 (0.30,0.74)	0.94 (0.64,1.23)	1.03 (0.66,1.39)	1.76 (1.33,2.18)	0.64 (0.55,0.74)

STEPH study group, JTH 2014

Agenda

DIAGNOSI Si può prescindere da una indagine strumentale ? E' necessario ripetere l'indagine dopo il trattamento ?

TERAPIA Come curarla? Terapia uguale per tutti ?

CONDIZIONI PARTICOLARI

- Neoplasia
- Recidiva
- Coinvolgimento della crosse safeno-femorale
- Gravidanza

DIAGNOSI

Si può prescindere da una indagine strumentale?

E' necessario ripetere l'indagine dopo il trattamento ?

Real life : .....in fase acuta

Table 2: Initial and follow-up imaging studies for diagnosing SVT among practitioners in North America and the global community.

Variable	North America, *n* (%)	Global Community, *n* (%)	*P* value
Type of initial duplex ultrasound			0.046
Bilateral lower extremity	181 (49.6%)	71 (58.2%)	
Unilateral lower extremity	145 (39.7%)	42 (34.4%)	
No ultrasound needed	22 (6%)	7 (5.7%)	
No answer	17 (4.7%)	2 (1.6%)	
After diagnosis of saphenous SVT, repeat ultrasound			0.88
1 week or less	105 (28.8%)	39 (32%)	
1–4 weeks	63 (17.3%)	23 (18.9%)	
1–3 months	52 (14.3%)	11 (9%)	
Only if symptoms worsen	62 (17%)	17 (13.9%)	
Other/no answer	83 (22.7%)	32 (26.2%)	
After diagnosis of SVT of superficial tributaries, repeat ultrasound			0.30
1 week or less	74 (20.3%)	28 (23%)	
1–4 weeks	64 (17.5%)	23 (18.9%)	
1–3 months	50 (13.7%)	19 (15.6%)	
Only if symptoms worsen	95 (26%)	28 (23%)	
Other/no answer	82 (22.5%)	24 (19.7%)	

Dua, Hindawi publishing corporation thrombosis 2014

Concomitante TVP o EP alla presentazione

Study	POST[1]	OPTIMEV[2]	STEPH [3]
Setting	Secondary/tertiary	Secondary/tertiary	Primary
N. of SVT patients	844	788	171
Concomitant DVT or PE	24.9%	29.4%	26.3%
Concomitant DVT	23.5%	28.8%	24.6%
Concomitant symptomatic PE	3.9%	6.8%	4.7%

Systematic research of PE symptoms and ultrasonography

Decousus et al, Ann Intern Med 2010;
Lalanaud e al, Thromb Haemost 2011.
Frappé et al Thromb Haemost 2014.

Nel caso di sospetto clinico di TVP sembra ragionevole raccomandare l'esecuzione di un test ultrasonografico entro 24-48 ore e iniziare una terapia con EBPM in caso di elevata probabilità

Profilo di Rischio

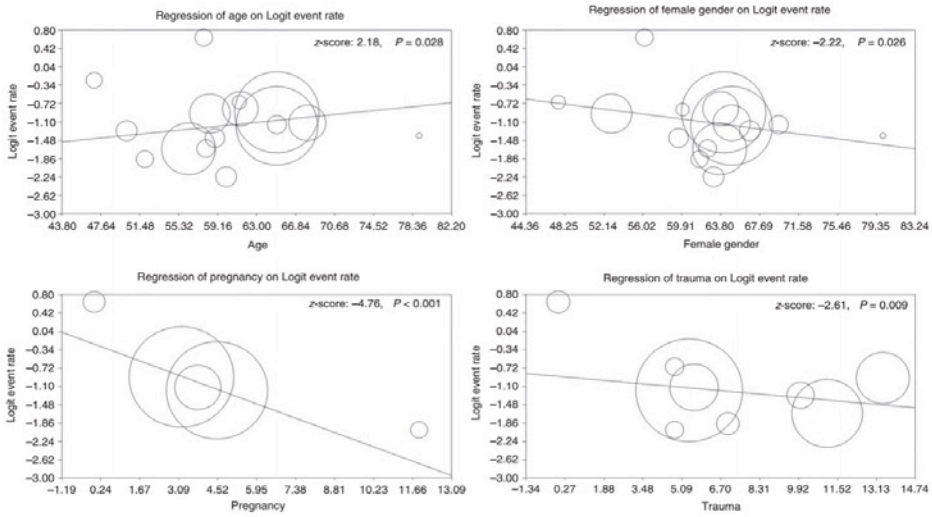


Fig. 3. Meta-regression analysis. Effect of age, female gender, recent trauma and pregnancy on the prevalence of deep vein thrombosis/pulmonary embolism in patients with superficial vein thrombosis.

Di Minno, JTH 2016

ICARO score

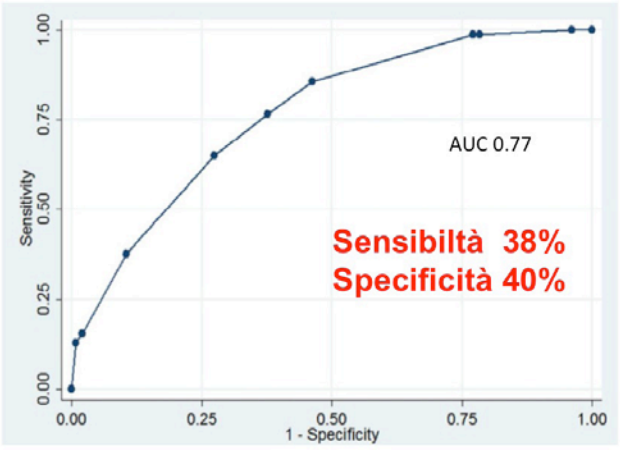
E' possibile predire la presenza di DVT nei pazienti affetti da SVT?

Table 2
Multivariate analysis of possible predictors of coexistence of DVT.

Characteristics	OR (95% CI)	Points assigned in the ICARO score
Cancer	3.49 (1.61, 7.55)	1.5
Edema of the limb	3.44 (1.99, 5.93)	1.5
Rope-like sign	0.38 (0.19, 0.41)	−1
Age over 50 years old	2.34 (1.23, 4.44)	1
Idiopathic SVT	0.48 (0.26, 0.87)	−1
Absence of varicose veins	1.81 (0.95, 3.47)	–

OR, odds ratio; CI, confidence interval.

Bassa <0 = DVT 1.1%
Intermedia 0-1 DVT 12%
Alta 32> DVT 1,5



Pomero, Thrombosis Research 2015

Real life.....il controllo

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Non è suggerito un controllo routinario in assenza di peggioramento clinico

Dua, Hindawi publishing corporation thrombosis 2014

Natura spontanea o provocata?

-**Non provocata** se non è possibile identificare nessun fattore scatenante

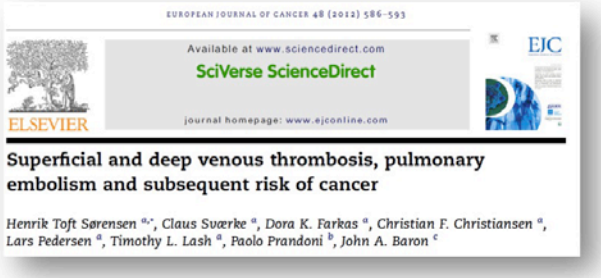
-**Provocata** se è possibile riconoscere un fattore di rischio tra quelli noti (immobilizzazione prolungata , neoplasia , chirurgia ect)

La presenza di vene varicose è un fattore di rischio per TVS

Fattori di rischio

- **Presenza di vene varicose (fattore principale, nell'80% dei casi)**
- Età avanzata
- Chirurgie
- Cancro attivo
- Gravidanza
- Terapia ormonale
- Obesità
- Malattie autoimmuni (Bechet e Buerger)
- Trombofilia

La ricerca di neoplasia occulta può essere giustificata in pazienti con forme spontanee? Valutare caso per caso?


EUROPEAN JOURNAL OF CANCER 48 (2012) 586–593

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

EJC

ELSEVIER

Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer

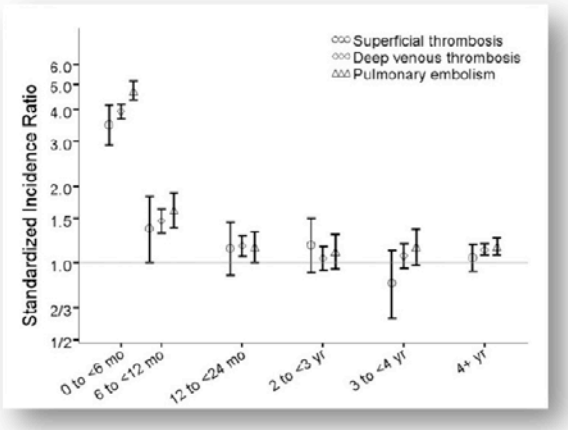
Henrik Toft Sørensen [a,], Claus Sværke [a], Dora K. Farkas [a], Christian F. Christiansen [a], Lars Pedersen [a], Timothy L. Lash [a], Paolo Prandoni [b], John A. Baron [c]*

- **2.4%** (95% CI, 2.10-2.86) per la TVS
- **2.75%** (95% CI, 2.60-2.90) per la TVP
- **3.27%** (95% CI, 3.03-3.52) per l'EP

Forte associazione per cancro del fegato, polmone, pancreas, ovaio, linfomi

DANISH REGISTRY

77.247 Pazienti
45.252 TVP,
24.332 EP,
7.663 TVS,
168 TVS + TVP,
97 TVS + EP



TERAPIA

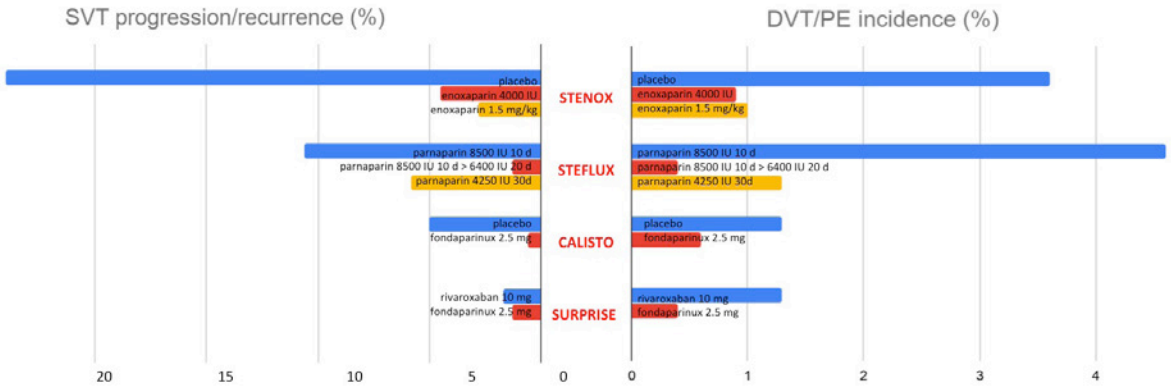
Come curarla? L'approccio terapeutico è uniforme?

Table 4: Anticoagulation trends among practitioners in North America and the global community.

Variable	North America, *n* (%)	Global community, *n* (%)	*P* value
Anticoagulation for patients with acute GSV SVT			0.84
All patients	34 (9.3%)	12 (9.8%)	
Involvement of >5 cm GSV	37 (10.1%)	16 (13.1%)	
Clot within 10 cm of saphenofemoral junction	101 (27.7%)	34 (27.9%)	
Proximal extension of clot on follow-up visit	91 (24.9%)	25 (20.5%)	
Never	41 (11.2%)	15 (12.3%)	
Other/no answer	61 (16.7%)	20 (16.4%)	
Anticoagulation for patients with acute SSV SVT			0.10
All patients	48 (13.2%)	11 (9%)	
Involvement of >5 cm SSV	44 (12%)	13 (10.7%)	
Clot with 10 cm of saphenofemoral junction	68 (18.6%)	25 (20.5%)	
Proximal extension of clot on follow-up visit	75 (20.6%)	38 (31.2%)	
Never	50 (13.7%)	11 (9%)	
Other/no answer	80 (21.9%)	24 (19.7%)	
Duration of initial anticoagulation for acute SVT			0.14
1 month or less	69 (18.9%)	28 (23%)	
1–3 months	95 (26%)	38 (31.2%)	
4–6 months	60 (16.4%)	17 (13.9%)	
>6 months	44 (12.1%)	13 (10.7%)	
Other/no answer	97 (26.6%)	26 (22.1%)	

Dua, Hindawi publishing corporation thrombosis 2014

Outcomes



Cochrane Library

Cochrane Database of Systematic Reviews

Treatment for superficial thrombophlebitis of the leg (Review)

In conclusion, fondaparinux appears to be an adequate treatment for most people with ST. The optimal dose and duration of treatment need to be established in people at high risk as well as people at low risk for recurrent thrombotic events. Further research is needed to assess the role of rivaroxaban and other such medicines, or thrombin, low molecular weight heparin or NSAIDs and to demonstrate the effectiveness, if any, of topical treatment, or surgery in terms of VTE.

Di Nisio, Cochrane Database of Systematic Reviews 2018

Durata e dose ottimale della terapia : a tutti 45 giorni?
A tutti la medesima posologia ?

Nessun trattamento antitrombotico nelle **TVS < 5cm?** Neppure se coinvolgono più segmenti o sono bilaterali?

Nelle forme **non provocate?** Su vena **«sana»**?

In coloro che hanno già sofferto di un **pregresso TEV** ?

Non ci sono al momento dati della letteratura a supporto di un prolungamento della durata della terapia o che l'incremento della dose migliori l'efficacia

Profilo di rischio dei pazienti inclusi nei differenti trial

Profilo di rischio %	Marchiori et al	STENOX	VESALIO	STEFLUX	CALISTO	SURPRISE
N	60	427	164	664	3002	472
Storia di TEV	10-13	15	Non noto	38	7	48.5
Storia di cancro	6-10	<2	Escluso	Escluso	Escluso	9.5
Età > 65 aa	45	circa 55	Non noto	Non noto	Non noto	37.3
Sesso maschile	Non noto	circa 40	<30	37	circa 35	circa 40
TVS in vena non varicosa	Non noto	Non noto	30	35	12	30

Jan Beyer-Westerndorf, Hematology 2017

Incidenza dell'endpoint primario (estensione o recidiva di TVS, TEV sintomatico o mortalità da tutte le cause) dopo la sospensione dei farmaci

CALISTO				SURPRISE			
Fondaparinux (n=1502)		Placebo (n=1500)		Rivaroxaban (n=236)		Fondaparinux (n=236)	
Giorno 47	Giorno 77	Giorno 47	Giorno 77	Giorno 45	Giorno 90	Giorno 45	Giorno 90
13 (0.9%)	18 (1.2%)	88 (5.9%)	94 (6.3%)	7 (3%)	15 (7%)	4 (2%)	15 (7%)

Pazienti con TVS isolata sono a rischio significativo di susseguente TVP o EP sintomatica a 3-6 mesi

Studio/setting	Trattamento	TVP(%)	EP(%)
STENOX 3 mesi N 427	EBPM per 12 gg nel 50%	2.8	0.7
VESALIO 3 mesi N164	EBPM per 30 gg in tutti	2.4	0.6
POST 3 mesi N 600	Uno o più anticoagulanti nel 90% (EBPM per una media di 11 gg)	2.8	0.5
OPTIMEV 3 mesi N 499	Anticoagulanti nel 76% (per 45 gg nel 24%)	0.6	0.6
CALISTO 77gg N 1.500	Placebo (esclusi pazienti ad alto rischio)	1.3	0.4
STEFLUX 3 mesi N 648	EBPM per 10-30gg in tutti	3.1	0.3
Van Weert 6 mesi N 185	Nessun trattamento nell'80%	2.7	0.5
Danish Registry 3 mesi N 10.9073	Nessun trattamento anticoagulante di routine	2.5	0.9

TVS senza concomitante TVP o EP alla presentazione

Decousus, J Thromb and Haemost 2015

Meta-analisi

DVT/PE incidence

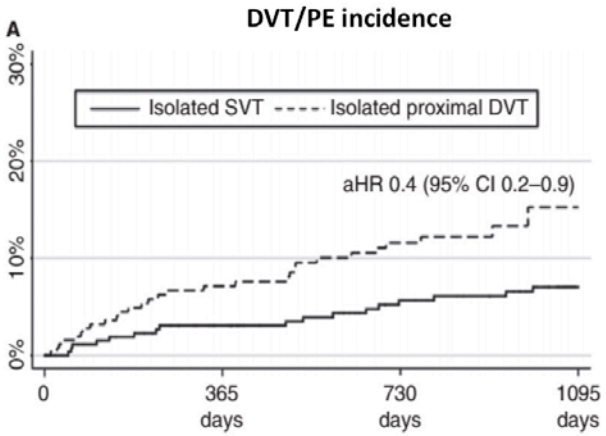
Treatment	Events per 100 patient-years (95% confidence interval)	I^2
NSAIDs	9.6 (2.1–21.8)	14%
LMWH low/prophylactic dose	12.1 (6.2–19.6)	45%
LMWH intermediate/ full dose	11.9 (6.8–18.2)	38%
UFH any dose	16.6 (1.6–43.0)	80%
Fondaparinux	1.4 (0.5–2.8)	18%
Warfarin	11.7 (3.3–59.5)	83%
Rivaroxaban low/ prophylactic dose	11.0 (4.3–20.2)	–
Surgery	12.1 (5.9–20.2)	0%
No therapy	10.5 (3.0–22.0)	67%

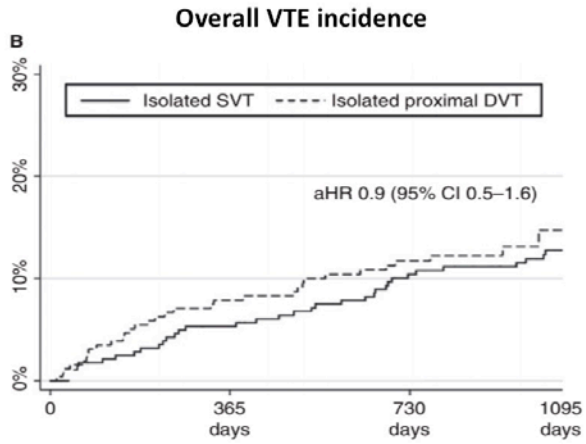
Other outcomes incidence

Treatment	PE	DVT	Extension or recurrent SVT	Bleeding	Death
NSAIDs	4.43 (0.38–12.57)	8.47 (2.09–18.58)	48.62 (28.81–68.66)	1.57 (0.06–7.43)	n/a
LMWH low/ prophylactic dose	2.9 (0.97–5.8)	10.4 (5.3–16.9)	26.5 (12.5–43.5)	0.1 (0.01–2.9)	0.1 (0.01–2.9)
LMWH intermediate/ full dose	2.37 (0.79–4.78)	10.72 (6.07–16.19)	33.59 (17.04–52.55)	0.81 (0.06–2.44)	0.64 (0.01–2.32)
UFH any dose	2.88 (0.20–8.53)	15.17 (1.67–38.61)	35.23 (9.17–67.41)	1.59 (0.25–8.87)	1.59 (0.25–8.87)
Fondaparinux	0.10 (0.00–0.58)	1.44 (0.53–2.79)	7.71 (1.86–17.05)	0.33 (0.03–0.98)	0.48 (0.08–1.22)
Warfarin	1.48 (0.32–8.78)	11.68 (3.34–59.54)	14.78 (1.35–38.84)	n/a	n/a
Rivaroxaban low/ prophylactic dose	0.00 (0.00–3.68)	10.97 (4.33–20.16)	17.74 (9.12–28.46)	0.42 (0.39–3.68)	0.42 (0.39–3.68)
Surgery	4.66 (0.50–12.73)	7.42 (1.98–15.92)	11.40 (0.04–38.55)	n/a	n/a
No therapy	1.92 (0.74–3.62)	10.09 (2.10–23.08)	62.98 (2.22–197.25)	0.49 (0.03–1.49)	0.49 (0.03–1.49)

Duffet, Thrombosis Hemostasis 2019

Complicanze nel follow-up





Galanaud , JTH 2017

Studio /setting	Trattamento ricevuto	Symptomatic thromboembolic complications
STENOX **Randomized trial, N = 427**	LMWH low dose LMWH high dose NSAID Placebo For 8-12 days	DVT or PE at 3 months: 3.3% DVT: 2.8%; PE: 0.7%
VESALIO [34] **Randomized trial, N = 164**	LMWH low dose LMWH high dose For 30 days	DVT or PE at 3 months: 3.1% DVT: 2.4%; PE: 0.6%
POST [12] **Prospective observational study, N = 600**	One or more anticoagulant: 90.5% LMWH high (62.9%) of low (36.7%) dose for 11 days VKA: 16.8% for 81 days Oral NSAID (8.2%) and surgery (10.2%)	Thromboembolic complications at 3 months: 8.3% DVT: 2.8% (half being proximal); PE: 0.5% SVT extension: 3.3% (irrespective of distance to the SFJ) SVT recurrence: 1.9%
OPTIMEV [16] **Prospective observational study, N = 499**	Anticoagulants: 76.4% (for > 45 days: 24.6%) LMWH only: 53.5% LMWH + VKA: 29.9%	DVT: 0.6%; PE: 0.6%; SVT recurrence: 1.8%
CALISTO [13,37] **Randomized trial (placebo group), N = 1500**	Placebo	Thromboembolic complications at 77 days: 9.4% DVT: 1.3%; PE: 0.4% DVT or PE: 1.5% SVT extension: 7.3% (≤ 3 cm from the SFJ: 3.6%; > 3 cm from the SFJ: 3.7%) SVT recurrence: 1.7%
STEFLUX [35] **Randomized trial, N = 648**	LMWH intermediate dose for 10 days: 32.7% LMWH intermediate dose for 30 days: 33.8% LMWH low dose for 30 days: 33.5%	DVT or PE at 3 months: 3.4% DVT: 3.1%; PE: 0.3%

Decousus, J Thromb and Haemost 2015

Condizioni Particolari

Neoplasia

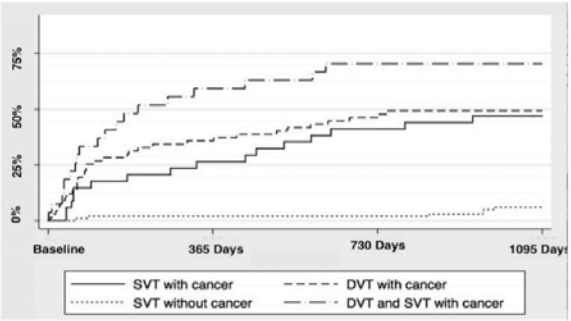
Recidiva

Coinvolgimento della crosse safeno-femorale

Gravidanza

Cancer associated thrombosis

Mortality after SVT



DVT/PE incidence after SVT

	Incidence %PY [95% CI]	HR [95% CI]
Cancer-related SVT	6.0 [2.2–15.9]	Reference
Cancer-related DVT	7.5 [3.9–14.5]	1.2 [0.4–4.0]
SVT without cancer	1.4 [0.5–3.7]	0.3 [0.07–1.0]
Cancer with SVT and DVT	16.2 [6.7–38.9]	2.3 [0.6–8.8]
Varicose veins	–	–
Anticoagulant treatment	–	–

Conclusion: Our results suggest that cancer patients with SVT have a poor prognosis, similar to that of patients with cancer-related DVT. The high rate of DVT-PE recurrence suggests that such patients may need longer duration of anticoagulant treatment.

Galanaud, Thrombosis Research 2018

Cancer associated thrombosis

- For patients experiencing SVT in the context of cancer, we suggest considering on a case-by-case basis prolongation of anticoagulant treatment beyond 45 days.
- In the event of symptomatic extension of SVT, objectively confirmed by ultrasound, in a patient receiving anticoagulant treatment at a prophylactic dose, we suggest continuing anticoagulant treatment at a curative dose for 3 months without switching to an oral anticoagulant.

Quéré, Journal Médecine Vasculaire 2018

Recidiva

Consensus French Society for Vascular Medicine (SFMV)

Non vi è indicazione a **trattamento anticoagulante prolungato** nel caso della **prima recidiva**

Il **trattamento anticoagulante prolungato** può essere preso in considerazione a partire dalla **terza recidiva**, condividendo con il paziente benefici e rischi dello stesso. Con quale farmaco? A che dose? Per 12 settimane?

Quéré, Journal Médecine Vasculaire 2018

Coinvolgimento della crosse safeno-femorale

	Placebo group (N = 1500)	
	Extension to ≤3 cm from the SFJ	Extension to >3 cm from the SFJ
Treatment received during the study, no. (%)		
Graduated compression stockings	46 (3.1)	51 (3.4)
Analgesic agents	16 (1.1)	22 (1.5)
Topical nonsteroidal antiinflammatory drugs	17 (1.1)	30 (2.0)
Topical anticoagulant drugs	5 (0.3)	8 (0.5)
Oral nonsteroidal antiinflammatory drugs/anti-cox 2	12 (0.8)	13 (0.9)
Aspirin or other antiplatelet agents	17 (1.1)	15 (1.0)
Anticoagulant treatment*	29 (1.9)	30 (2.0)
High (therapeutic dose)	19 (1.3)	17 (1.1)
Intermediate dose	1 (0.1)	2 (0.1)
Low (prophylactic dose)	14 (0.9)	14 (0.9)
Unknown dose	1 (0.1)	1 (0.1)
Face-to-face visit after event diagnosis (in addition to those planned by the protocol), no. (%)	34 (2.3)	24 (1.6)
Compression ultrasonography to follow up this event after diagnosis, no. (%)	19 (1.3)	29 (1.9)

	Placebo group (N = 1500)	
	Extension to ≤3 cm from the SFJ	Extension to >3 cm from the SFJ
Hospitalization after event diagnosis, no. (%)	33 (2.2)	22 (1.5)
Duration, days (mean ± standard deviation)	6.4 ± 6.3	6.6 ± 4.3
Surgery to treat SVT, no. (%)†	34 (2.3)	20 (1.3)
No surgery to treat SVT, no. (%)	19 (1.3)	36 (2.4)
and no anticoagulant treatment either	6 (0.4)	14 (0.9)

Trattamento anticoagulante a dosi terapeutiche per 3 mesi, da preferire all'intervento di legatura

Leizorovic, Blood 2013

Gravidanza

CLINICAL GUIDELINES blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

- LMWH vs nessun trattamento
- durata del trattamento: per il resto della gravidanza e per 6 settimane nel post-parto
- intensità del trattamento: dose profilattica, dose intermedia, dose di attacco intermedia seguita da dose profilattica?
- fondaparinux non indicato poichè attraversa la barriera emato-placentare

Terapie non farmacologiche

- terapia elastocompressiva, FANS
- legatura della crosse safeno-femorale
- legatura e stripping della vena coinvolta
- legatura delle perforanti

Scarsità di RCT, studi molto differenti per tipi di trattamento, criteri di inclusione, outcomes.

→ terapia chirurgica non raccomandata sistematicamente. Necessaria valutazione caso per caso.

Agenda

DIAGNOSI Si può prescindere da una indagine strumentale ? Timing? E' necessario ripetere l'indagine dopo il trattamento ? Ricerca di neoplasia occulta nelle forme non provocate?

TERAPIA Come curarla? l'approccio terapeutico deve essere uguale per tutti?

CONDIZIONI PARTICOLARI

- Neoplasia (dose e durata)
- Recidiva
- Gravidanza (farmaco, dose e durata)
- Coinvolgimento della crosse safeno-femorale

«Possiamo lamentarci perché i cespugli di rose hanno le spine , o gioire perchè i cespugli spinosi hanno le rose»
Abraham Lincoln

Grazie e …. buon lavoro!

Epidemiologia

Table 5 Risk factors for the development of deep vein thrombosis (DVT)/pulmonary embolism (PE) in patients diagnosed with acute symptomatic isolated superficial vein thrombosis (iSVT)

	No. of patients with DVT/PE	Unadjusted HR (95% CI)	Adjusted HR (95% CI)Model A	Adjusted HR (95% CI)Model B
Off anticoagulant treatment	49	2.55 (0.79–8.20)	2.93 (0.90–9.45)	2.60 (0.74–9.19)
On anticoagulant treatment	3	Reference	Reference	Reference
Age > 65 years (n = 137)	45	0.99 (0.97–1.01)*	–	0.99 (0.97–1.01)*
Age ≤ 65 years (n = 274)	7	–	–	–
Male sex (n = 157)	26	1.77 (1.03–3.06)	2.03 (1.16–3.54)	1.99 (1.13–3.48)
Female sex (n = 254)	26	Reference	–	Reference
Prior DVT/PE (n = 68)	8	0.72 (0.34–1.54)	–	0.96 (0.42–2.22)
No prior DVT/PE (n = 343)	44	Reference	–	Reference
Family history of VTE (n = 129)	22	1.25 (0.72–2.17)	–	1.10 (0.62–1.96)
No family history of VTE (n = 282)	30	Reference	–	Reference
Saphenofemoral junction involvement (n = 19)	1	0.37 (0.05–2.68)	–	0.38 (0.05–2.94)
No saphenofemoral junction involvement (n = 392)	51	Reference	–	Reference
Active solid cancer (n = 24)	4	2.64 (0.94–7.41)	3.12 (1.11–8.93)	4.62 (1.48–14.42)
No active solid cancer (n = 387)	48	Reference	Reference	Reference
Unprovoked iSVT (n = 191)	23	1.07 (0.62–1.85)	–	1.23 (0.69–2.19)
Provoked iSVT (n = 220)	29	Reference	–	Reference

CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism. Model A was based on backward stepwise selection for $P < 0.10$ in univariate regression analysis. Model B was adjusted for all of the covariates described. *Expressed per unit of increase.

Barco, JTH 2017

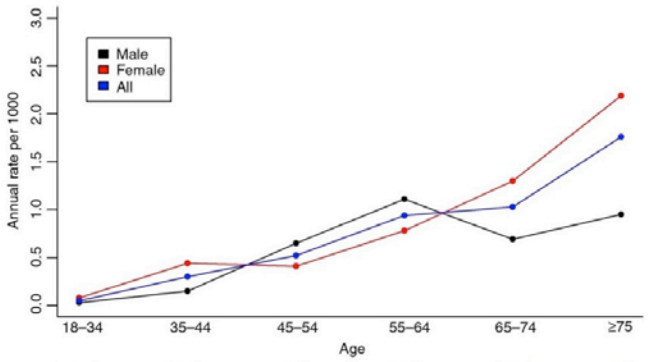
Catheter related thrombosis

Table 4. Multivariate/Adjusted Analysis for Effect of Line Type on Thrombosis Events.

	MC Adjusted[a]	PICC Adjusted[a]	AOR (95% CI)[b]	*P* Value
Catheter-related events				
Thrombosis (DVT or SVT)	22.30%	12.34%	2.04 (1.46-2.86)	<.0001
DVT	12.53%	6.85%	1.95 (1.28-2.97)	.0019
SVT	5.56%	2.91%	1.96 (1.18-3.25)	.0090

Bahl, Clinical and Applied Thrombosis/Hemostasis 2019

Epidemiologia



AGE (years)	18–34	35–44	45–54	55–64	65–74	≥75	Total
Men							
Cases	1	3	13	22	9	12	60
Rate/1000 (95% CI)	0.03 (0.00,0.08)	0.15 (0.00,0.32)	0.65 (0.30,1.00)	1.11 (0.65,1.58)	0.69 (0.24,1.14)	0.95 (0.41,1.48)	0.49 (0.36,0.61)
Women							
Cases	3	9	9	17	21	52	111
Rate/1000 (95% CI)	0.08 (0.00,0.17)	0.44 (0.15,0.73)	0.41 (0.14,0.67)	0.78 (0.41,1.15)	1.30 (0.74,1.85)	2.19 (1.59,2.78)	0.78 (0.63,0.92)
Total							
Cases	4	12	22	39	30	64	171
Rate/1000 (95% CI)	0.05 (0.00,0.10)	0.30 (0.13,0.46)	0.52 (0.30,0.74)	0.94 (0.64,1.23)	1.03 (0.66,1.39)	1.76 (1.33,2.18)	0.64 (0.55,0.74)

STEPH study group, JTH 2014