ANTICOAGULANTI NELLE TROMBOSI VENOSE SUPERFICIALI

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PATHOGENESIS AND TREATMENT OF SUPERFICIAL VEIN THROMBOSIS

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INTERNAL MEDICINE DEPARTMENT
Piacenza Hospital

Il *sottoscritto* *Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- ALFA WASSERMANN
- BAYER
- BOHERINGER INGELHEIM
- DAIICHI-SANKYO
- IL
- KEDRION
- PFIZER
- SANOFI AVENTIS

EVIDENCE: HOW SHOULD WE TREAT SVT?

Dott. Davide Imberti

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INTERNAL MEDICINE DEPARTMENT
Piacenza Hospital

My talk today

- Evidence with LMWHs
- The CALISTO Study
- Guidelines
- Conclusions

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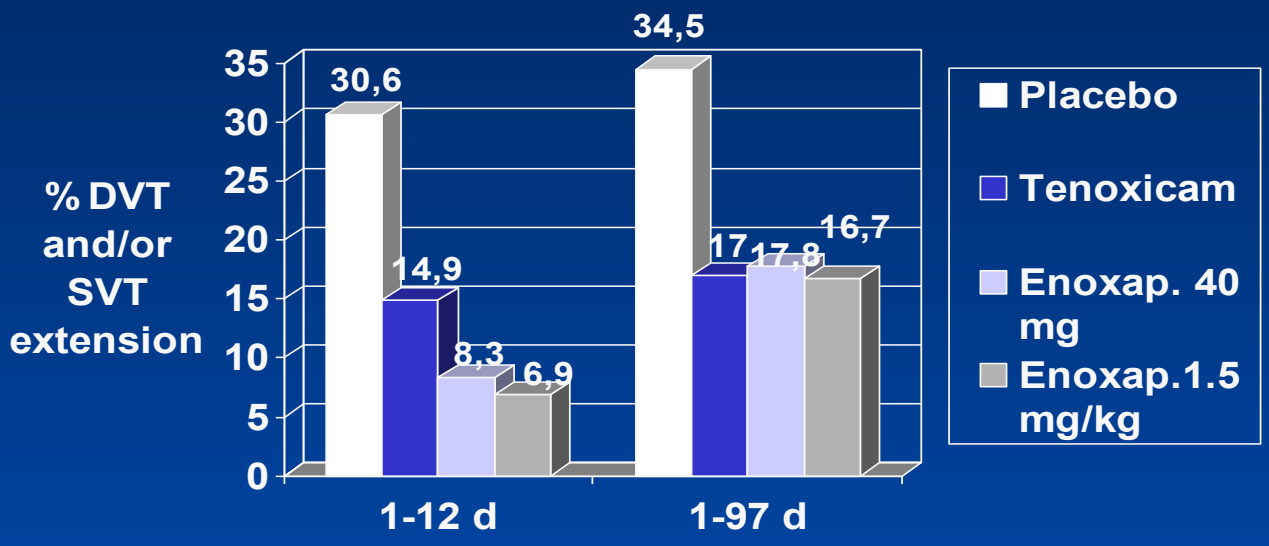
THE RANDOMIZED, DOUBLE-BLIND STENOX STUDY



Decousus H et al. for the STENOX Investigators Group. Arch Intern Med 2003;163:1657-63.

High vs. low doses of low-molecular-weight heparin for the treatment of superficial vein thrombosis of the legs: a double-blind, randomized trial

THE VESALIO INVESTIGATORS GROUP[1]

Prospective, controlled, randomized, double-blind, multicenter

Group high-dose (treatment; n=83) =
- 0.3 ml placebo +
- weight adjusted nadroparin (19.000 a-Xa IU ml) x 10 d
  half dose " " x 20 d

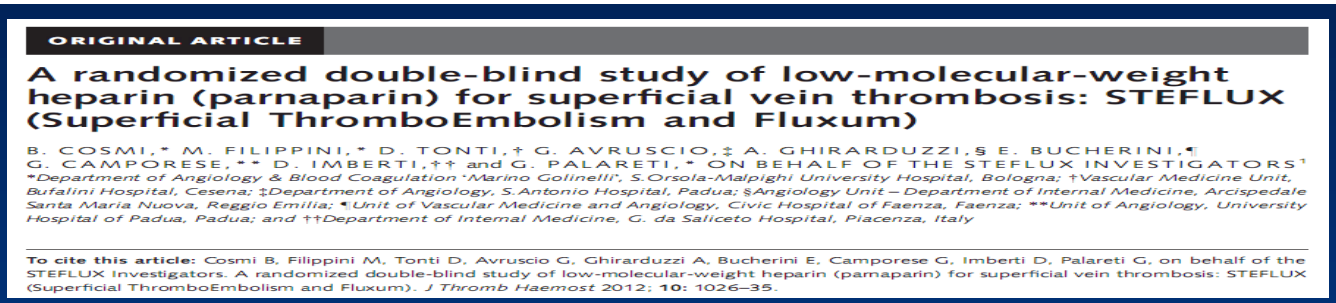
Group low-dose (prophylaxis; n=81) =
- 0.3 ml nadroparin (+ 2850 a-Xa IU) x 30 d +
- placebo

Prandoni P et al. for the VESALIO Investigators Group. J Thromb Haemost 2005;3:1152-7.

RESULTS

	Low dose (n=83)	High dose (n=81)
DVT/PE/SVT ext	8.6 %	7.2 %
Major bleeding	0 %	0 %

Prandoni P et al. for the VESALIO Investigators Group. J Thromb Haemost 2005;3:1152-7.



ORIGINAL ARTICLE

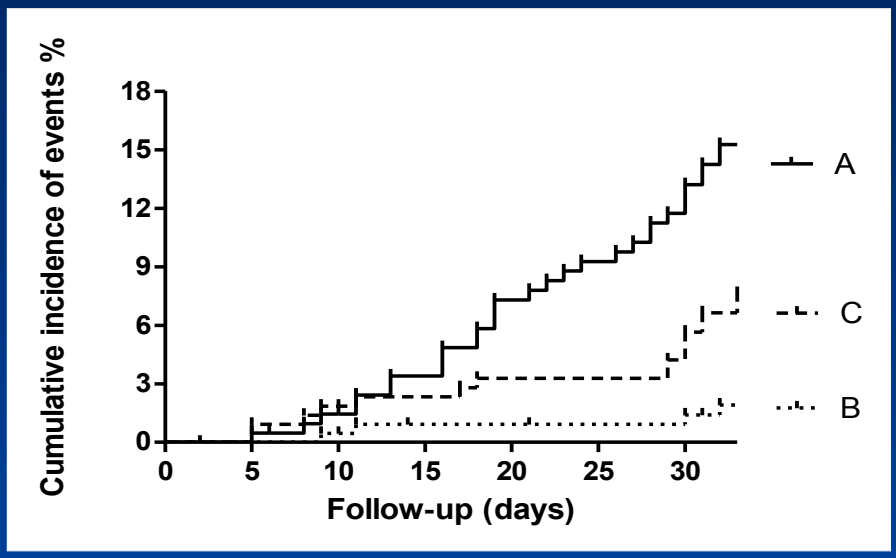
A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum)

B. COSMI,* M. FILIPPINI,* D. TONTI,† G. AVRUSCIO,‡ A. GHIRARDUZZI,§ E. BUCHERINI,¶ G. CAMPORESE,** D. IMBERTI,†† and G. PALARETI,* ON BEHALF OF THE STEFLUX INVESTIGATORS

*Department of Angiology & Blood Coagulation "Marino Golinelli", S.Orsola-Malpighi University Hospital, Bologna; †Vascular Medicine Unit, Bufalini Hospital, Cesena; ‡Department of Angiology, S.Antonio Hospital, Padua; §Angiology Unit – Department of Internal Medicine, Arcispedale Santa Maria Nuova, Reggio Emilia; ¶Unit of Vascular Medicine and Angiology, Civic Hospital of Faenza, Faenza; **Unit of Angiology, University Hospital of Padua, Padua; and ††Department of Internal Medicine, G. da Saliceto Hospital, Piacenza, Italy

To cite this article: Cosmi B, Filippini M, Tonti D, Avruscio G, Ghirarduzzi A, Bucherini E, Camporese G, Imberti D, Palareti G, on behalf of the STEFLUX Investigators. A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum). *J Thromb Haemost* 2012; **10:** 1026–35.

Follow-up was 60 days



Cumulative incidence of events in the first 33 days of treatment in the 3 groups
Logrank test for trend P=0.0018 Log-rank (Mantel-Cox) Test p=< 0.0001
A VS B P=< 0.0001 B VS C:P= 0.006

Cosmi B et al. on behalf of the STEFLUX Investigators Group. J Thromb Haemost 2012;10:1026-35.

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The NEW ENGLAND JOURNAL of MEDICINE
2010;363:1222-32

ORIGINAL ARTICLE

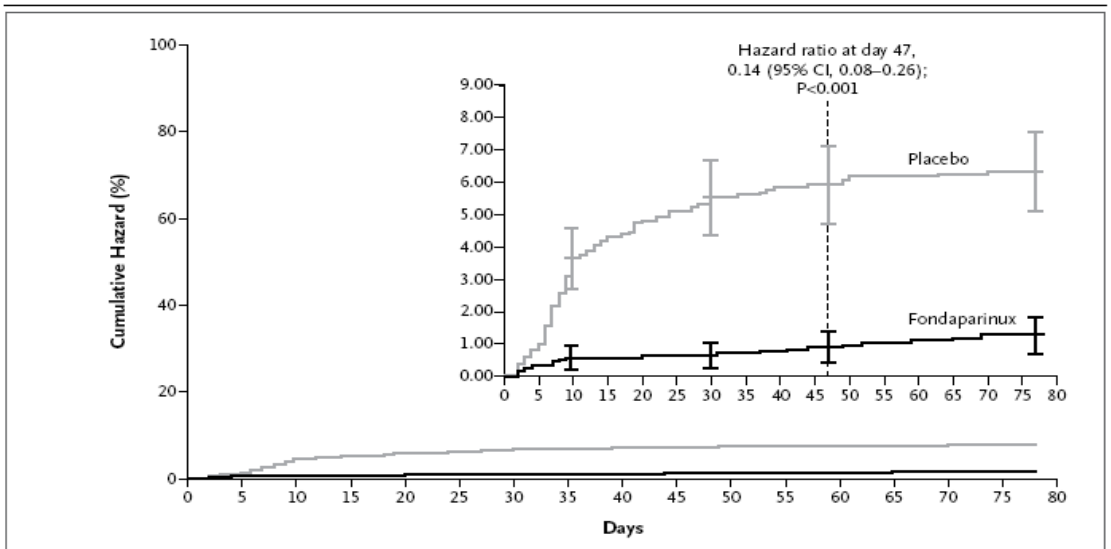
Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs

Hervé Decousus, M.D., Paolo Prandoni, M.D., Ph.D., Patrick Mismetti, M.D., Ph.D., Rupert M. Bauersachs, M.D., Zoltán Boda, M.D., Benjamin Brenner, M.D., Silvy Laporte, Ph.D., Lajos Matyas, M.D., Saskia Middeldorp, M.D., Ph.D., German Sokurenko, M.D., and Alain Leizorovicz, M.D., for the CALISTO Study Group*

Multicenter, randomized, double-blind, controlled vs placebo on efficacy and safety of Fondaparinux (Arixtra) for the treatment of SVT

Patients enrolled : 3.002
Inclusion: SVT confirmed with CUS, > 5 cm length
Exclusion: SVT < 3 cm from saphenous-femoral cross, thrombotic events < previous 6 months, active cancer, warfarin, NSAIDs, recent bleeds, platelets <100.000 plt/dl), Cr Cl< 30 ml/min

Treatments: Fondaparinux 2,5 mg or Placebo
Duration: 45 d
Follow-up: 1 month



No. at Risk	Day 10±2	Day 30±2	Day 45±2	Day 75±2
Placebo	1437	1399	1388	1330
Fondaparinux	1483	1477	1468	1410

Figure 1. Kaplan–Meier Estimates of the Probability of the Primary Efficacy Outcome, According to Study Group.
The primary efficacy outcome was a composite of death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis. Data from patients who were lost to follow-up were censored at the time of the last contact. I bars indicate 95% confidence intervals.

Decousus H et al. N Engl J Med 2010;363:1222-32.

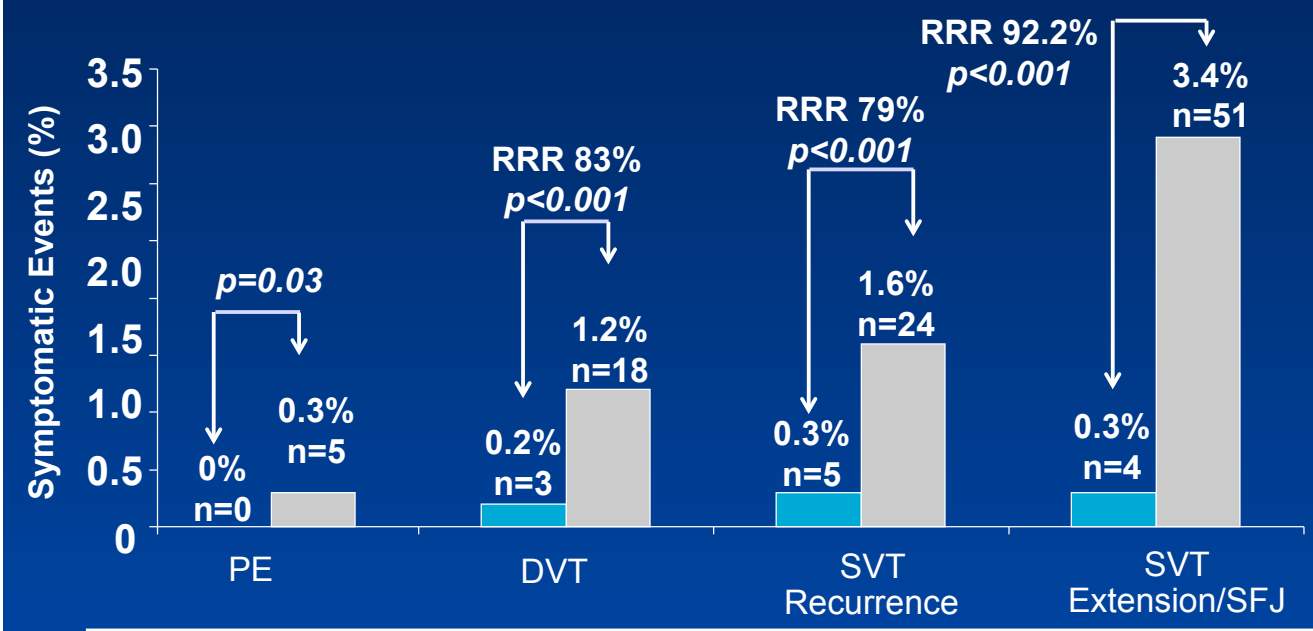
Table 3. Efficacy Outcomes.

Efficacy Outcome	Fondaparinux (N=1502)	Placebo (N=1500)	Absolute Risk Reduction with Fondaparinux	Relative Risk with Fondaparinux	P Value*
	no. with event (%)		*percentage points (95% CI)*	*% (95% CI)*	
By Day 47					
Primary composite outcome†	13 (0.9)	88 (5.9)	−5.0 (−6.3 to −3.7)	0.15 (0.08 to 0.26)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	5 (0.3)	−0.3 (−0.6 to 0.0)	Not calculated	0.03
Deep-vein thrombosis¶	3 (0.2)	18 (1.2)	−1.0 (−1.6 to −0.4)	0.17 (0.05 to 0.56)	<0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	4 (0.3)	51 (3.4)	−3.1 (−4.1 to −2.2)	0.08 (0.03 to 0.22)	<0.001
Recurrence of superficial-vein thrombosis	5 (0.3)	24 (1.6)	−1.3 (−2.0 to −0.6)	0.21 (0.08 to 0.54)	<0.001
Deep-vein thrombosis or pulmonary embolism	3 (0.2)	20 (1.3)	−1.1 (−1.8 to −0.5)	0.15 (0.05 to 0.50)	<0.001
Surgery for superficial-vein thrombosis	11 (0.7)	57 (3.8)	−3.1 (−4.1 to −2.0)	0.19 (0.10 to 0.37)	<0.001
By Day 77					
Composite outcome†	18 (1.2)	94 (6.3)	−5.1 (−6.4 to −3.7)	0.19 (0.12 to 0.32)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	6 (0.4)	−0.4 (−0.7 to −0.1)	Not calculated	0.02
Deep-vein thrombosis	4 (0.3)	19 (1.3)	−1.0 (−1.6 to −0.4)	0.21 (0.07 to 0.62)	0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	5 (0.3)	54 (3.6)	−3.3 (−4.3 to −2.3)	0.09 (0.04 to 0.23)	<0.001
Recurrence of superficial-vein thrombosis	8 (0.5)	26 (1.7)	−1.2 (−2.0 to −0.4)	0.31 (0.14 to 0.68)	0.002
Deep-vein thrombosis or pulmonary embolism	4 (0.3)	22 (1.5)	−1.2 (−1.9 to −0.5)	0.18 (0.06 to 0.53)	<0.001
Surgery for superficial-vein thrombosis	15 (1.0)	61 (4.1)	−3.1 (−4.2 to −1.9)	0.25 (0.14 to 0.43)	<0.001

* P values were calculated with the use of Fisher's exact test.
† Some patients had more than one event.
‡ There were two deaths from cancer in the fondaparinux group and one death from acute heart failure in the placebo group.
§ No instance of pulmonary embolism was fatal.
¶ There were 11 cases of proximal deep-vein thrombosis: 1 in the fondaparinux group and 10 in the placebo group.

No difference for bleeding between treatment and placebo

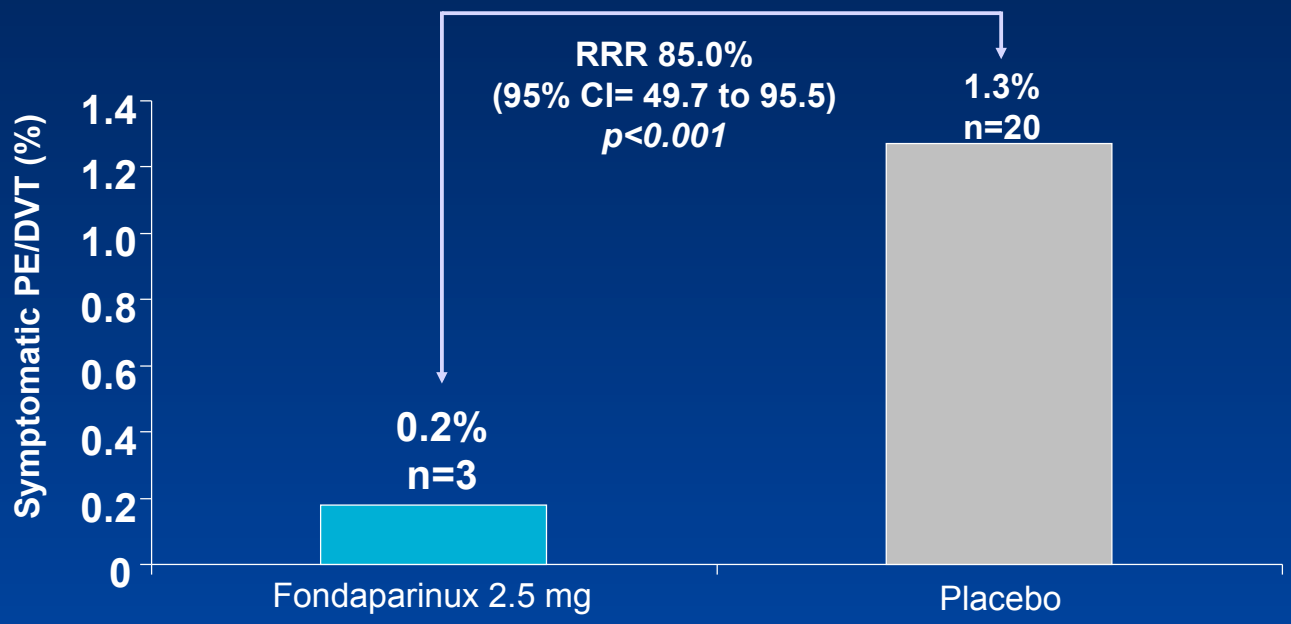
Secondary Efficacy Outcomes (Day 47)



Some patients underwent two outcomes. Death: Fondaparinux=2 (cancer); Placebo=1 (heart failure)

Decousus H et al. N Engl J Med 2010;363:1222-32.

Symptomatic PE or DVT (Day 47)



Symptomatic proximal DVT: Fondaparinux=1; Placebo=10
Symptomatic PE: Fondaparinux=0; Placebo=5

Decousus H et al. N Engl J Med 2010;363:1222-32.

Safety Outcomes (Day 47)

	Fondaparinux N=1499	Placebo N=1488
Major bleeding	1 (0.1%)	1 (0.1%)
Fatal bleeding	0	0
Clinically relevant non-major bleeding	5 (0.3%)	8 (0.5%)
Minor bleeding	9 (0.6%)	6 (0.4%)
All bleeding	15 (1.0%)	14 (0.9%)

Some patients experienced more than one event

Decousus H et al. N Engl J Med 2010;363:1222-32.

CALISTO:

Strength

High number of patients

Placebo controlled

Very good results

Weakness

Only 30 d. FU

Only symptomatic complications

Treatment for superficial thrombophlebitis of the leg.

Di Nisio M et al *Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD004982*

- 26 RCTs, 5521 participants
- Methodological quality of most of the trials: poor.
- Fondaparinux, LMWH, UFH, NSAIDs, topical treatment, oral treatment, intramuscular treatment, and intravenous treatment to surgery.

- Prophylactic dose fondaparinux given for six weeks appears to be a valid therapeutic option for ST of the legs.

- Further research to assess the role of new oral anticoagulants, LMWH and NSAIDs; the optimal doses and duration of treatment; and whether a combination therapy may be more effective than single treatment.

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9th ACCP Consensus

(Kearon C et al. Chest 2012;141(2)(Suppl):e419S–e494S)

8.1.1. In patients with SVT ….of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B) **.**

8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)

9th ACCP Consensus

(Kearon C et al. Chest 2012;141(2)(Suppl):e419S–e494S)

Factors that favor the use of anticoagulant therapy in patients with SVT include:

- **extensive SVT**
- **involvement above the knee, particularly if close to the saphenofemoral junction**
- **severe symptoms**
- **involvement of the greater saphenous vein**
- **history of VTE or SVT**
- **active cancer**
- **recent surgery**

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CONCLUSIONS

- SVTs require anticoagulant treatment
- LMWH = relatively high dose
- Fondaparinux = prophylactic dose for 45 days, treatment of choice
- Some SVT still have late complications after 30 d of treatment
  How to identify these patients?

CONCLUSIONS

- SVTs require anticoagulant treatment
- LMWH = relatively high dose
- Fondaparinux = prophylactic dose for 45 days , treatment of choice
- Class II elastic stockings
- Some SVT still have late complications after 30 d of treatment
How to identify these patients?
- Evaluation of individual risk factors