COME TRATTARE I PAZIENTI COMPLESSI CON TROMBOSI VENOSE

LA TERAPIA DELLA TROMBOSI VENOSA SUPERFICIALE

DAVIDE IMBERTI

MEDICINA INTERNA
CENTRO EMOSTASI E TROMBOSI
OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

Il *sottoscritto Imberti Davide*

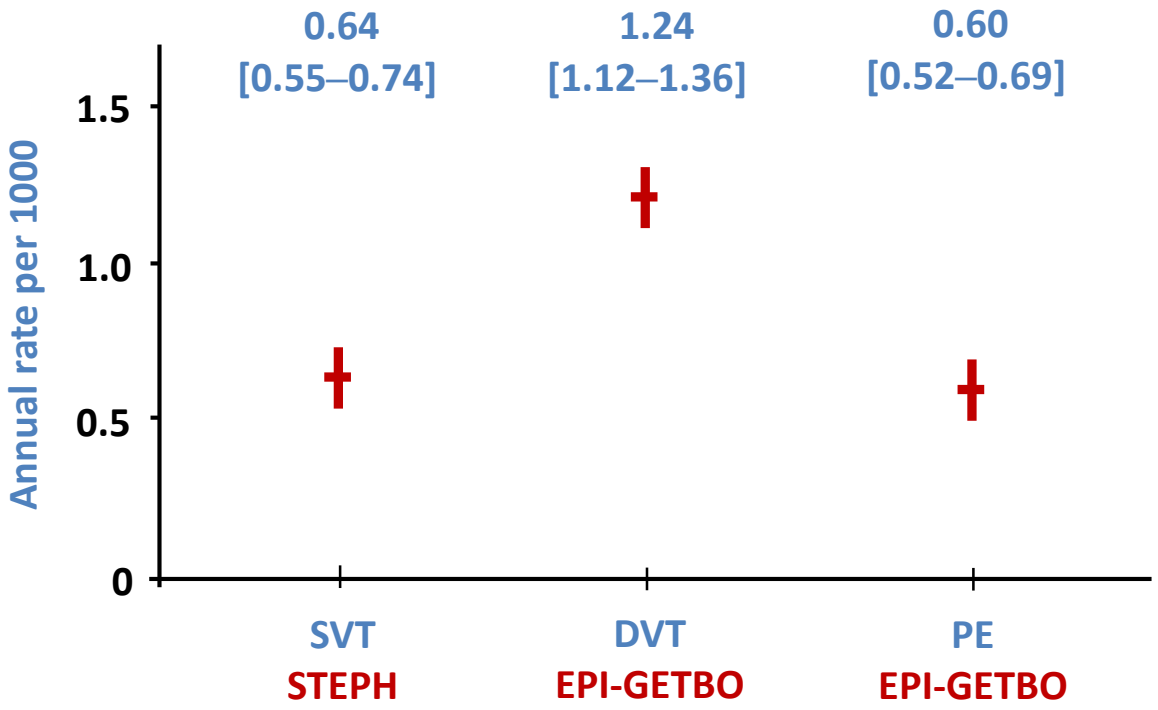
dichiara

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

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

SVT is a frequent disease

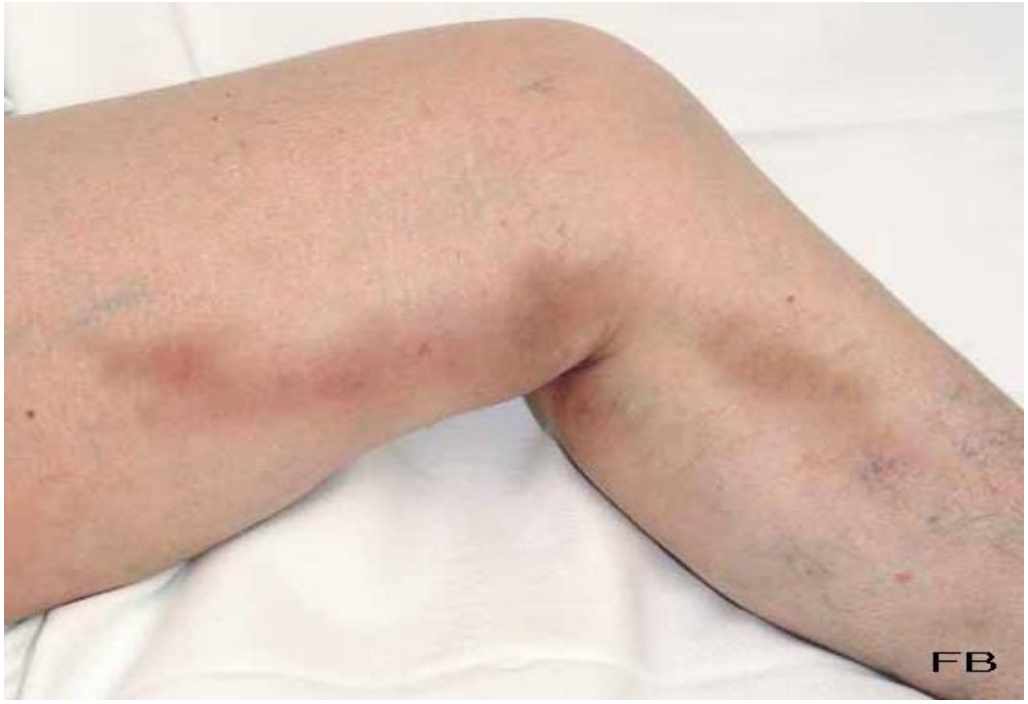
STEPH[1] and EPI-GETBO[2]: Two French prospective epidemiological studies with comparable methodology



1. Frappé P. et al. J Thromb Haemost 2014; 12:831–838.
2. Oger E. Thromb Haemost 2000; 83:657–660.

DVT = deep vein thrombosis; PE = pulmonary embolism;
SVT = superficial vein thrombosis.

SVT: A thrombus in a superficial vein with an inflammatory component



Often associated with pain and impaired mobility

Treatment is needed to relieve local symptoms when present:

- Analgesics
- Topical NSAIDS
- Compression stockings

Is this kind of treatment sufficient?

Decousus et al. J Thromb Haemost 2015

NSAIDs = non-steroidal anti-inflammatory drugs;
SVT = superficial vein thrombosis.

Concomitant DVT or PE is frequent in patients with SVT at first presentation

Study	POST [1.4]	OPTIMEV [2,4]	STEPH [3,4]
Setting	Secondary/tertiary	Secondary/tertiary	Primary
No. 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

**40 to 50% are proximal DVT, 40 to 45% are non-contiguous to SVT*

→ **Systematic research of PE symptoms and ultrasonography**

1. Decousus H. et al. Ann Intern Med 2010; 152:218–24.
2. Galanaud JP. et al. Thromb Hemost 2011; 105:31–39.
3. Frappé P. et al. J Thromb Hemost 2014; 12:831–838.
4. Decousus H. et al. J Thromb Haemost 2015; 13 Suppl 1:S230–237.

DVT = deep vein thrombosis; PE = pulmonary embolism; SVT = superficial vein thrombosis.

Patients with isolated SVT* are at significant risk of subsequent symptomatic DVT or PE at 3–6 months

Study/setting	Treatment received	DVT, %	PE, %
STENOX 3 months, N = 427	**LMWH for 12 days in 50%**	**2.8**	**0.7**
VESALIO 3 months, N = 164	**LMWH for 30 days in all**	**2.4**	**0.6**
POST 3 months, N = 600	**One or more anticoagulants in 90.5%** (LMWH for a median of 11 days)	**2.8**	**0.5**
OPTIMEV 3 months, N = 499	**Anticoagulants in 76.4%** (for > 45 days in 24.6%)	**0.6**	**0.6**
CALISTO* 77 days, N = 1,500	**Placebo** (patients at high risk excluded)	**1.3**	**0.4**
STEFLUX 3 months, N = 648	**LMWH for 10–30 days in all**	**3.1**	**0.3**
Van Weert 6 months, N = 185	**No treatment in 83%**	**2.7**	**0.5**
Danish Registry 3 months, N = 10,973	**No routine anticoagulant treatment**	**2.5**	**0.9**

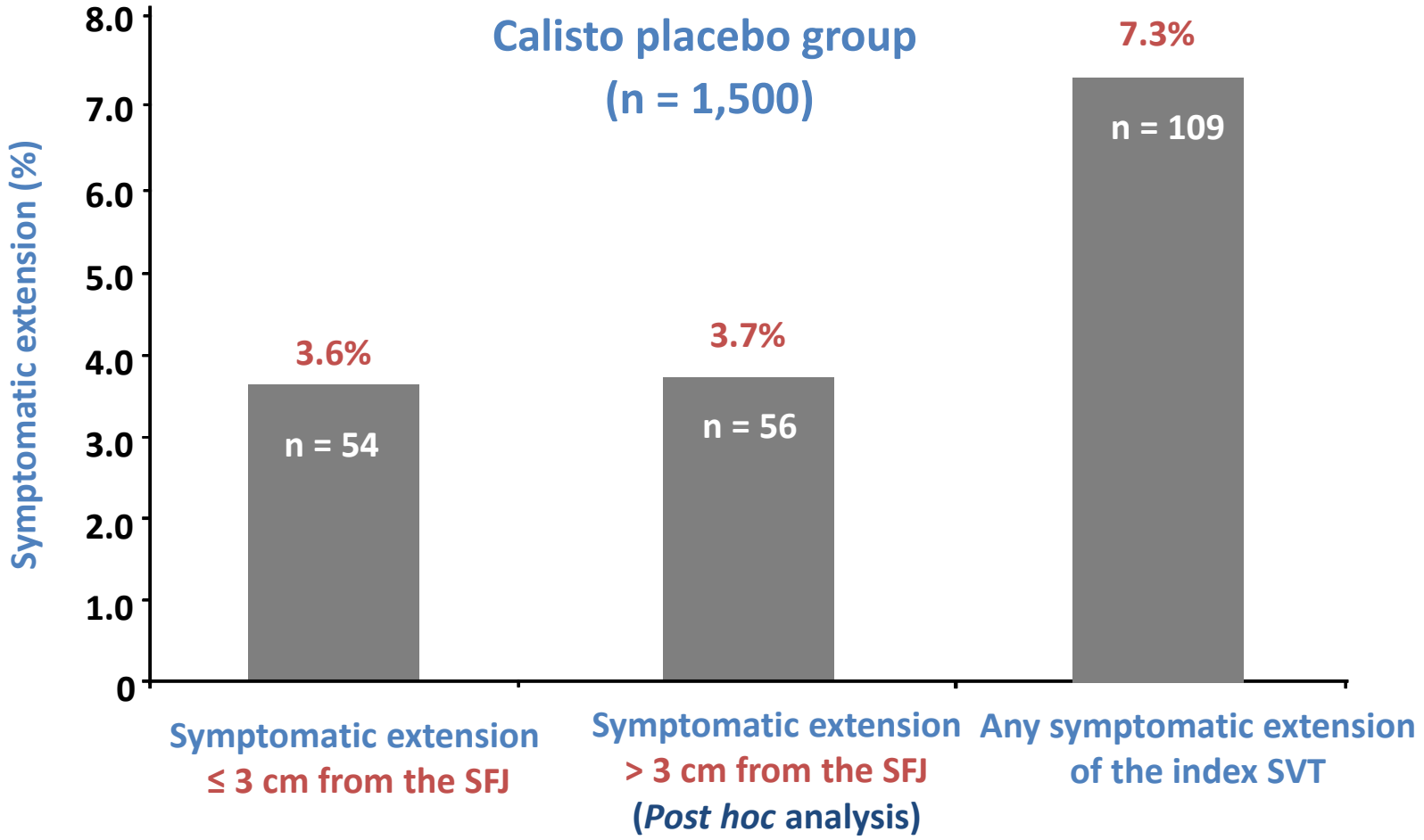
**** SVT without concomitant DVT or PE at first presentation.***

DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SVT = superficial vein thrombosis.

1. Decousus H. et al. J Thromb Haemost 2015; 13 Suppl 1:S230–237.

Patients with isolated SVT are at significant risk of subsequent symptomatic SVT extension

(All confirmed by CUS and central blind adjudication)

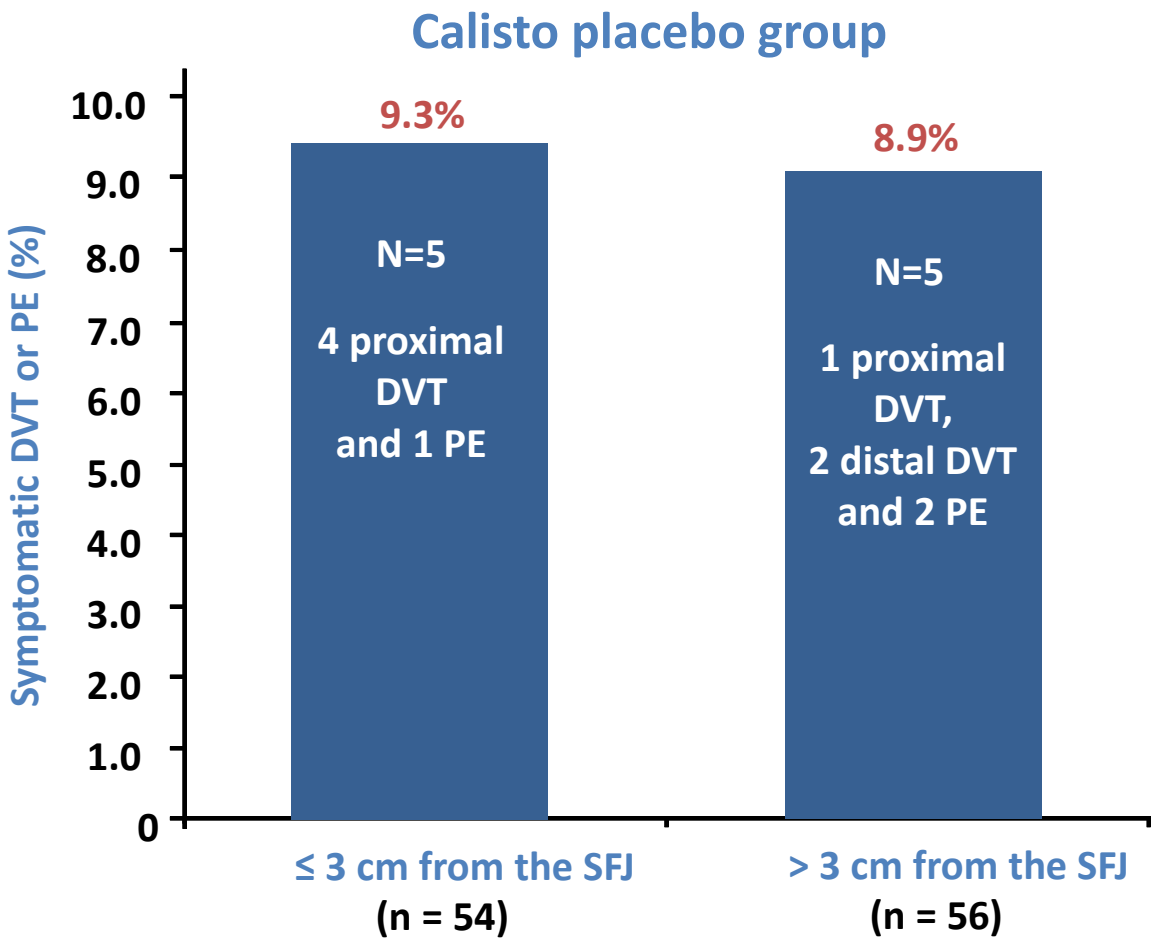


Decousus H. et al, for the CALISTO Study Group. N Engl J Med 2010; 363:1222–1232.

Leizorovicz A. et al. Blood 2013; 122:1724–1729.

CUS = compression ultrasonography; DVT = deep vein thrombosis; SFJ = sapheno-femoral junction; SVT = superficial vein thrombosis.

Despite medical management, SVT extensions, whether or not reaching the SFJ, are associated with increased risk of subsequent symptomatic DVT or PE



(*Post hoc* analysis)

DVT = deep vein thrombosis;
PE = pulmonary embolism;
SFJ = sapheno-femoral junction;
SVT = superficial vein thrombosis.

Leizorovicz A. et al. Blood 2013; 122;1724–1729.

Independent risk factors for symptomatic or asymptomatic DVT/PE/SVT extension/recurrence at 3 months

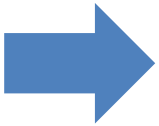
Mutivariate analyses from STENOX[1] (n = 413), POST[2] (n = 586), and STEFLUX[3] (n = 627)

- Interval between symptom onset and diagnosis ≤ 7 days[1]
- Male sex[1,2]
- Overweight[3]
- History of DVT or PE[1-3]
- History of cancer[2]
- Severe venous insufficiency[1]
- SVT in a non-varicose vein[2]

1. Quenet S. et al. J Vasc Surg 2003;38:944–949.
2. Decousus H. et al. Ann Intern Med 2010; 152:218–224.
3. Cosmi B. et al. for the STEFUX Investigators. Thromb Res 2014; 133:196–202.

DVT = deep vein thrombosis;
PE = pulmonary embolism;
SVT = superficial vein thrombosis.

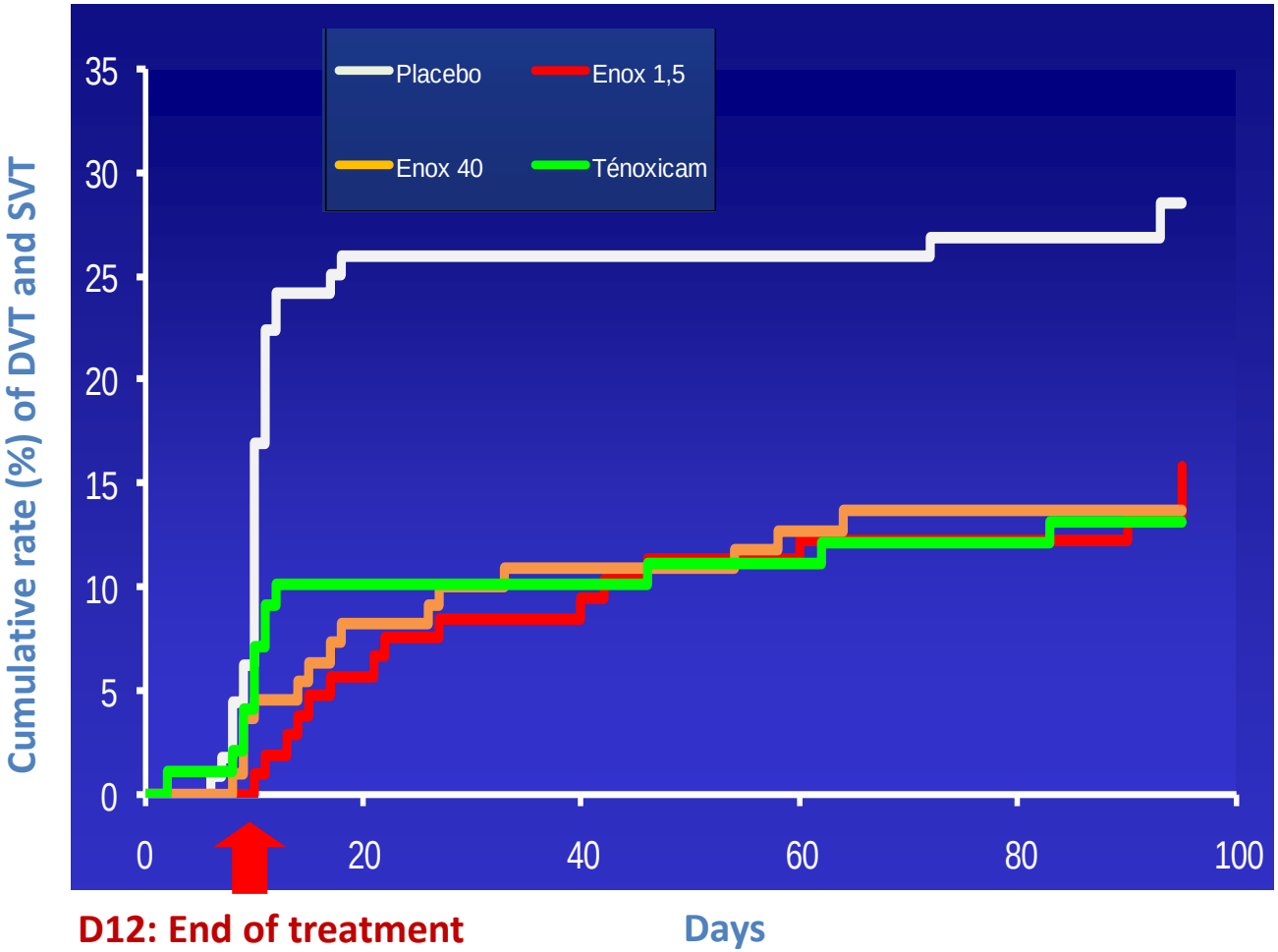
Anticoagulant therapy is needed to prevent symptomatic TE complications in patients with acute isolated SVT of the legs



- Which agent?
  - Dose?
  - Duration?
- Which patients?

SVT = superficial vein thrombosis;
TE = thromboembolic.

STENOX: 12 days of LMWH treatment is not sufficient – prophylactic and curative regimen seem as effective



Randomised, double-blind, 4-parallel-group trial (n = 427)

In the enoxaparin groups, the majority of VTE events occurred after the end of study treatment

DVT = deep vein thrombosis;
LMWH = low-molecular-weight heparin;
SVT = superficial vein thrombosis;
VTE = venous thromboembolism.

Decousus H. et al. for the STENOX Study Group. Arch Intern Med 2003; 163:1657–1663.

VESALIO: 30 days of LMWH treatment seems to be insufficient – an intermediate regimen seems more effective than a prophylactic regimen

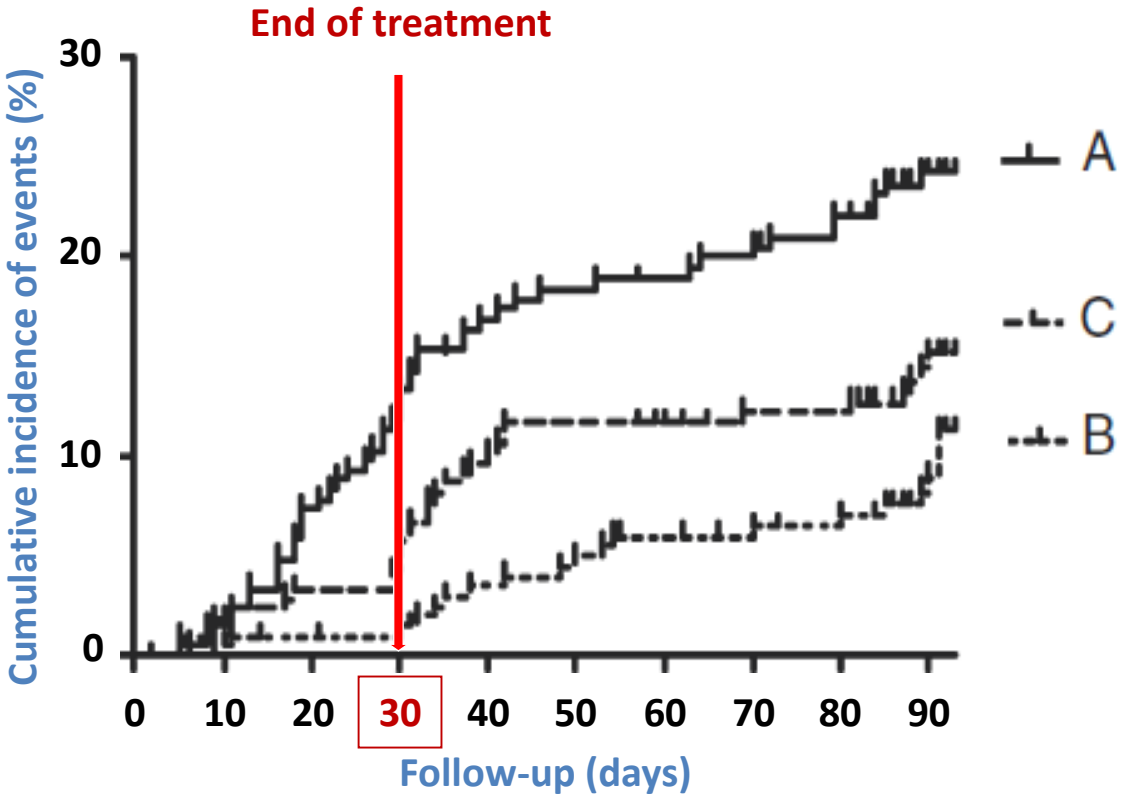
- Randomised, double-blind trial comparing 2 doses of nadroparin (n = 164)
- 70% of symptomatic VTE events occurred after the end of treatment (Day 30)

DVT/PE or extension of SVT	Nadroparin Prophylactic dose (n = 81)	Nadroparin High dose (n = 83)
Day 30 (end of treatment)	**5 (6.2%)**	**2 (2.4%)**
Events	*4 asympt. extensions* *1 **sympt.** extension*	*1 **sympt.** PE* *1 asympt. extension*
Day 90 (end of follow-up) – Primary endpoint	**7 (8.6%)**	**6 (7.2%) (NS)**
Additional events	*2 **sympt.** DVT*	*2 **sympt.** DVT* *1 asympt. DVT* *1 **sympt.** extension*

Asympt = asymptomatic; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SVT = superficial vein thrombosis; sympt = symptomatic.

Prandoni P. et al. J Thromb Haemost 2005; 3:1152–1157.

STEFLUX: 30 days of LMWH treatment seems to be insufficient – an intermediate regimen is more effective than a prophylatic regimen



Randomised, double-blind, 3-parallel-group trial (n = 664)

Comparison Day 0/Day 30

Log-rank test (trend): $P = 0.0018$
Log-rank test (Mantel-Cox): $P < 0.0001$
A vs. B: $P < 0.0001$
B vs. C: $P = 0.006$
A vs. C: $P = 0.0065$

Comparison Day 0/Day 90

Log-rank test (trend): $P = 0.0117$
Log-rank test (Mantel-Cox): $P < 0.0001$
A vs. B: $P < 0.0001$
B vs. C: $P = 0.06$
A vs. C: $P = 0.0019$

Cumulative incidence of events during treatment and follow-up (0–93 days)

A = Parnaparin 8500 aXa IU OD for 10 days followed by placebo for 20 days **(intermediate dose of LMWH for 10 days)**
B = Parnaparin 8500 aXa IU OD for 10 days followed by 6400 aXa IU OD for 20 days **(intermediate dose of LMWH for 30 days)**
C = Parnaparin 4250 aXa IU OD. for 30 days **(prophylactic dose of LMWH for 30 days)**

Cosmi B. et al. for the STEFUX Investigators. J Thromb Haemost 2012; 10:1026–1035.

LMWH = low-molecular-weight heparin;
IU = international units; OD = once daily.

The NEW ENGLAND JOURNAL of MEDICINE

2010;363:1222-32.

ORIGINAL ARTICLE

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

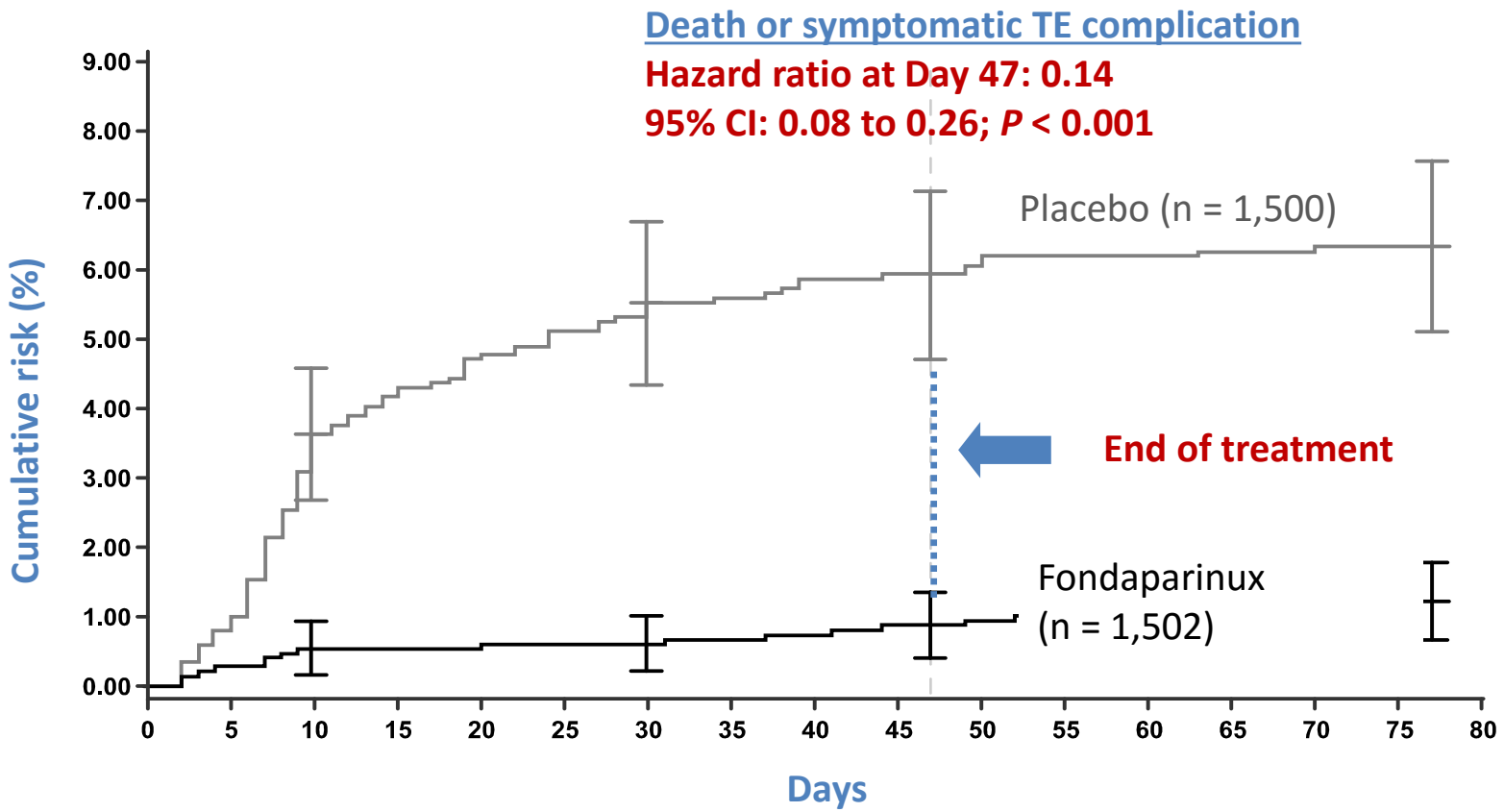
Hervé Decousus, M.D., Paolo Prandoni, M.D., Ph.D., Patrick Mismetti, M.D., Ph.D., Rupert M. Bauersachs, M.D., Zoltán Boda, M.D., Benjamin Brenner, M.D., Silvy Laporte, Ph.D., Lajos Matyas, M.D., Saskia Middeldorp, M.D., Ph.D., German Sokurenko, M.D., and Alain Leizorovicz, M.D., for the CALISTO Study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

45 days of 2.5 mg fondaparinux treatment is effective and does not lead to catch-up phenomena

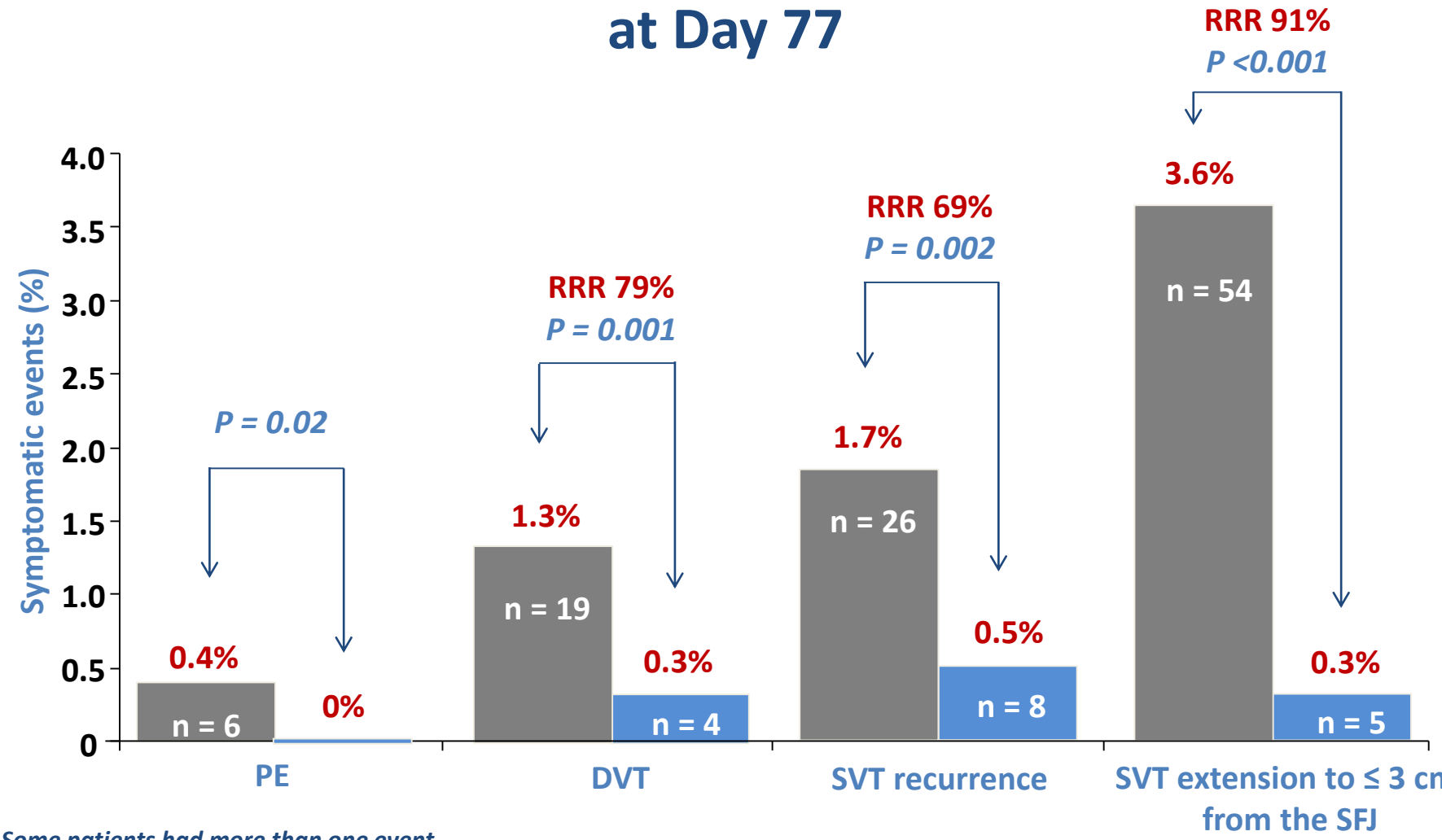


Without increasing the bleeding risk

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

TE = thromboembolic.

Fondaparinux reduced the risk of each TE component of the composite outcome at Day 77



Some patients had more than one event.
Death: fondaparinux = 2 (cancer); placebo = 1 (acute heart failure).

DVT = deep vein thrombosis;
RRR = relative risk reduction; SFJ = sapheno-femoral junction;
SVT = superficial vein thrombosis; TE = thromboembolic.

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

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

CALISTO

Strength

High number of patients

Placebo controlled

Very good results

Weakness

Only 30 d. FU

Only symptomatic complications

Patients resembling those included in CALISTO:

- Spontaneous acute symptomatic isolated SVT of the legs > 5 cm in length
- Head of thrombus > 3 cm from the SFJ
- No recent history of VTE, active cancer or pregnancy

→

- **Should receive 2.5 mg fondaparinux for 45 days**

SFJ = sapheno-femoral junction;
SVT = superficial vein thrombosis;
venous thromboembolism.

Personal communication.

Current recommendations

ACCP[1]

- For patients presenting with an SVT of the lower limbs at least 5 cm in length, we suggest treatment with fondaparinux or LMWH at prophylactic dose for 45 days, rather than no anticoagulation (Grade 2B)
- For patients receiving anticoagulation treatment for an SVT, we suggest use of fondaparinux 2.5 mg rather than LMWH at prophylactic dose (Grade 2C)

Cochrane review[2]

- For patients presenting with the most severe forms of SVT, such as those evaluated in CALISTO, the use of fondaparinux at prophylactic dose appears to be a valid therapeutic option at the dose of 2.5 mg/d for 45 days
- No definitive recommendations can be made concerning LMWH, UFH or NSAIDs

1. Kearon et al. Chest 2012; 141:e419S–e494S.
2. Di Nisio et al. Cochrane Database Syst Rev. 2013; 4:CD004982.

LMWH = low-molecular-weight heparin;
NSAIDs = non-steroidal anti-inflammatory drugs;
UFH = unfractionated heparin;
SVT = superficial vein thrombosis.

Limitations of available anticoagulant agents

- **LMWH**
  - Uncertainty on the optimal dose (intermediate/prophylactic?) and duration (45-day treatment not tested)
- **New oral anticoagulant agents**
  - No data (2 ongoing trials)
- **Fondaparinux**
  - Not evaluated in patients with recent history of VTE, active cancer and pregnancy
  - 30-day treatment not tested

LMWH = low-molecular-weight heparin;
VTE = venous thromboembolism.

Other unanswered questions

- Value of anticoagulation in patients with SVT < 5 cm in length
- Optimal management of patients with SVT involving the SFJ
- Optimal dose and duration of anticoagulation in patients with increased bleeding risk
- Management of patients with SVT of the upper limbs
- Optimal thromboprophylaxis strategy in patients with a history of SVT exposed to additional risk factors in a later life

SFJ = sapheno-femoral junction;
SVT = superficial vein thrombosis.