# Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism: a systematic review

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The aim of this systematic review was to summarize the evidence from randomized controlled trials (RCT) concerning the efficacy and safety of medical or surgical treatments of superficial vein thrombosis (SVT) for the prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE). A systematic search was performed in MEDLINE, EMBASE and the Cochrane (CENTRAL) database to identify all randomized trials that evaluated the effect of surgical or medical treatment in the prevention of venous thromboembolism (VTE) in patients with SVT of the legs. Five studies were included. Pooling of the data was not possible due to the heterogeneity among the studies. Moreover, three studies had major methodological drawbacks limiting the clinical applicability of the results. One of the remaining (pilot) studies showed a non-significant trend in favor of high- compared to low-dose unfractionated heparin for the prevention of VTE. The last remaining study showed a non-significant trend in favor of short-term treatment with low-molecular-weight heparin (LMWH) or a non-steroidal anti-inflammatory drug (NSAID) as compared to placebo shortly after treatment with respect to VTE, but the apparent benefit disappeared after three months of follow-up. Active treatment of SVT reduced the incidences of SVT extension or recurrence. Treatment with a therapeutic or prophylactic dose of LMWH or a NSAID reduces the incidence of SVT extension or recurrence, but not VTE. More RCT are needed before any evidence-based recommendations on the treatment of SVT for the prevention of VTE can be given.With the present lack of solid evidence we would suggest treating patients with at least intermediate doses of LMWH.

Key words: anticoagulants, non-steroidal anti-inflammatory agents, superficial vein thrombosis, thrombophlebitis, surgical treatment.

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Superficial vein thrombosis (SVT) is a common disease and although the incidence of SVT has never been properly assessed, it is estimated to be higher than that of deep vein thrombosis (DVT), which has an incidence of 1 per 1000 inhabitants per year.[1-3] Predisposing risk factors for SVT are very similar to those observed for venous thromboembolism (VTE) and include varicose veins, postoperative states, pregnancy, active malignancies, auto-immune diseases, use of oral contraceptives and a history of previous VTE.[4-16,17] Furthermore, the presence of inherited thrombophilia (e.g. factor V Leiden, the prothrombin 20210A mutation and deficiencies of the natural anticoagulant proteins C and S) in SVT suggest a similar etiology.[2,8,12,14,15]

Traditionally, SVT has been considered a relatively benign disease. However, several studies have described an association of SVT with VTE. In patients with a diagnosis of SVT, 6-44% of cases are associated with DVT, 20-33% with asymptomatic pulmonary embolism (PE) and 2-13% with symptomatic PE.[5,6,11,18-27] SVT located in the main trunk of the saphenous vein has the strongest association with VTE.[6,11,18-20,23,26,28-30] The variation in estimates reported in literature is probably due to the retrospective character of most studies, the small number of patients included and the fact that SVT was often diagnosed in vascular laboratories, where patients were referred for suspected DVT. Conservative management, mainly focusing on the painful symptoms of disease, might therefore be insufficient. Until now, there has been no consensus about the optimal treatment of SVT in clinical practice. Several therapies have been pro-

posed, including surgical therapy (ligation or stripping of the affected veins), elastic stockings, non-steroidal anti-inflammatory drugs (NSAID) which aim to reduce pain and inflammation, and several anticoagulant agents.

We aimed to systematically review the evidence from randomized controlled trials (RCT) concerning the efficacy and safety of medical or surgical, but not topical, treatment for the prevention of VTE in SVT, as well as the progression and/or recurrence of SVT.

### Study identification

A computer-assisted search was performed to identify all RCT in all languages that evaluated the effect of surgical or medical treatment for the prevention of DVT and PE in patients with SVT of the legs.

Studies were identified by searching MEDLINE from 1966 until September 2004 with the following search terms: *randomized controlled trial, controlled clinical trial, random allocation, comparative study, clinical trial, thrombophlebitis, superficial thrombophlebitis, phlebitis, superficial thrombosis, saphenous vein thrombosis, saphenous thrombosis, saphenous phlebitis*. In addition, EMBASE was searched from 1980 until September 2004 with the following search terms: *clinical trial, randomized controlled trial, randomization, multi-center study, controlled study, crossover procedure, double blind procedure, single blind procedure, major clinical study, placebo, meta analysis, phase 2 clinical trial or phase 3 clinical trial/or phase 4 clinical trial, superfical adj1 thrombosis, thrombophlebitis, superficial thrombo, thrombophlebitis/, phlebitis/, saphenous adj1 thrombosis, saphenous phlebitis, saphenous vein thrombosis*. Finally, the Cochrane CENTRAL Database was searched using the key words: *superficial venous thrombosis, superficial vein thrombosis, thrombophlebitis, superficial thrombosis, superficial thrombophlebitis, saphenous vein AND thrombosis, saphenous vein AND thrombophlebitis, saphenous vein AND phlebitis*.

### Inclusion criteria

The following inclusion criteria were applied for the selection of the trials:

*Study design*. Randomized trials.

*Populations*. Patients with SVT of the lower limb(s) confirmed by ultrasonography.

*Interventions*. medical (unfractionated heparin (UFH); low-molecular-weight heparin (LMWH), in therapeutic or prophylactic doses; NSAID; vitamin K antagonists (VKA) (e.g. warfarin or coumadin) or surgical (stripping or ligation) treatment. Studies evaluating the effect of topical/local treatment only were not included.

*Efficacy outcomes*. VTE (DVT and PE) as objectively confirmed by ultrasound, venography or impedance plethysmography, progression and/or recurrence of SVT as objectively confirmed by ultrasound or venography during and directly after treatment and after 2, 3 and/or 6 months of follow-up.

*Safety outcomes*. All-cause mortality, major bleeding and if applicable heparin-induced thrombocytopenia.

*Follow-up*. All patients had to be clinically followed up after treatment.

### Study selection

Two reviewers (IW, MD) independently screened titles and abstracts from the database searches to determine whether the inclusion criteria appeared to be satisfied. Titles and abstracts that seemed relevant were selected and full articles were examined. References of all articles were cross-checked to identify additional articles. An effort was made to contact one of the authors in case the article could not be retrieved or lacked information. Discordances were dealt with by discussion with a third reviewer (SM).

### Data extraction

Data were extracted from the selected studies by two independent reviewers (IW, MD), using a data extraction form. Discordances were dealt with by discussion with a third reviewer (SM).

### Methodological quality of included studies

The methodological quality of included studies was assessed by considering the comparability of patient groups at baseline, the randomization method, allocation concealment, blinding of treatment from investigators and/or participants, use of a placebo group and completeness of follow-up using a standardized form.

### Statistical analysis and pooling

We planned to pool the results of the selected studies based on comparability of patient inclusion criteria and treatment regimens. For each study the relative risk (RR) with a 95% confidence interval (CI) for dichotomous data was calculated.

### Results

We analyzed five studies that fulfilled our inclusion criteria (Figure 1, Table 1). The studies were not considered comparable in terms of treatment regimens, so that the data were not pooled. Safety outcomes were available in four of the five included studies.

In the first randomized, open trial by Titon *et al*. three treatment regimens were compared (Table 1). [31] All 117 patients included wore elastic stockings for six days. The results of ultrasonography were available for 113 patients (97%) at day 7 and in 104 patients (89%) after eight weeks. No symptomatic PE or extension of the thrombus into the deep venous system occurred in the course of the trial. At

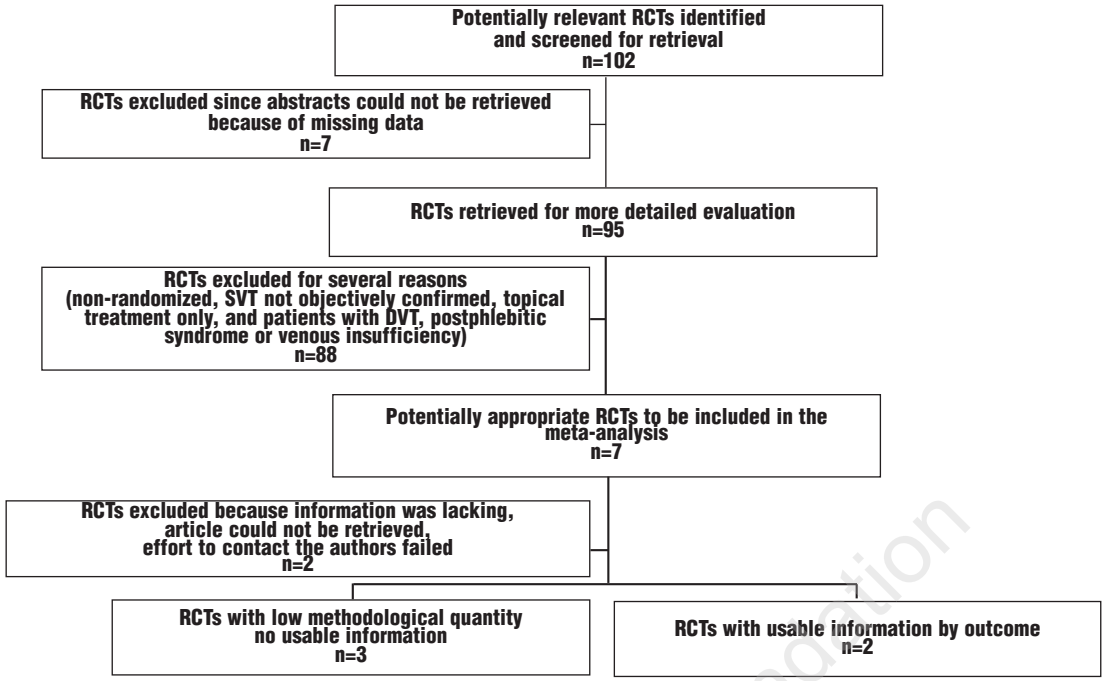


**Figure 1.** Flow chart of selected studies.



**Table 1.** Characteristics of included studies.

| *Study* | *Methods and quality°* | *Participants* | *Interventions* | *Outcomes* |
|---|---|---|---|---|
| Titon *et al.* (1994) | RCT, unblinded, no placebo; 8 weeks follow-up; dropout rate 11% Allocation concealment B | 117 participants; all SVT's | NSAID (naproxen), therapeutic fixed dose LMWH (nadroparin) or bodyweight adjusted dose of LMWH Treatment for 6 days | recurrence and/or extension of SVT and/or VTE directly after treatment and after 2 months |
| Belcaro *et al.* (1999) | RCT, unblinded, no placebo; 6 months follow-up; dropout rate 21% Allocation concealment B | 562 participants; only large varicose veins and SVT | ECS only, ECS+early surgery, ECS+proph.LMWH*/UFH, ECS+VKA (coumadin) Treatment duration unclear | recurrence and/or extension of SVT and/or directly after treatment and after 3 and 6 months |
| Marchiori*et al.* (2002) | pilot RCT, single blind, no placebo; 6 months follow-up; dropout rate 0% Allocation concealment A | 60 participants; only great saphenous vein SVT | twice daily s.c. injected high dose UFH (12.500 IU) for 1 week, followed by 10.000 IU or low dose UFH (5000 IU) Treatment for 4 weeks | recurrence and/or extension SVT and/or VTE directly after treatment and after 3 months |
| Stenox (2003) | pilot RCT, double blind, placebo controlled; 3 months follow-up; dropout rate 2% Allocation concealment A | 436 participants; all SVT's | prophylactic LMWH (enoxaparin), therapeutic LMWH. NSAID (tenoxicam) or placebo. Treatment for 8-12 days | recurrence and/or extension of SVT and/or VTE directly after treatment and after 3 months. |
| Lozano *et al.* (2003) | RCT, unblinded, no placebo; 6 months follow-up; dropout rate 5% Allocation concealment B | 60 participants; only great saphenous vein SVT"s above the knee | saphenofemoral disconnection or LMWH (enoxaparin) 1 mg/kg bodyweight twice daily for 1 week followed by the same dose once a day for 3 weeks | recurrence and/or extension of SVT and/or VTE after 1, 3 and 6 months. |

*RCT denotes randomized controlled trial; SVT, superficial vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; LMWH, low-molecular-weight heparin; VTE, venous thrombo-embolism; ECS, elastic compression stockings; s.c., subcutaneously; UFH, unfractionated heparin; Stenox, The Superficial Thrombophlebitis Treated by Enoxaparin Study Group. °Quality criteria: allocation concealment = adequate (A), unclear (B), inadequate (C) or not used (D). *The type of LMWH used in the trial is not mentioned in the article.*

**Table 2.** Absolute event rates and relative risks of the selected outcomes when comparing results of different treatments within each study.

| Study | Treatment | Duration of medical treatment (days) | Duration of follow-up treatment (months) | Absolute event rates at the end of follow-up No. of patients (%) | | RR (95% CI) | |
|---|---|---|---|---|---|---|---|
| | | | | VTE | SVT | VTE | SVT |
| Titon *et al.*[†] | NSAID | 6 | 2 | 0/33 (0.0) | 0/33 (0.0) | – | – |
| (1994) | therap.LMWH (f) | | | 0/36 (0.0) | 2/36 (5.6) | not estimable | not estimable |
| | therap.LMWH (a) | | | 0/35 (0.0) | 0/35 (0.0) | not estimable | not estimable |
| Belcaro *et al.*[§] | ECS | 9 | 6 | 6/78 (7.7) | 13/78 (16.7) | – | – |
| (1999) | ECS+ligation | | | 2/78 (2.6) | 6/78 (7.7) | 0.33 (0.07-1.60) | 0.46 (0.18-1.15) |
| | ECS+stripping | | | 2/70 (2.9) | 1/70 (1.4) | 0.37 (0.08-1.78) | 0.09 (0.01-0.64) |
| | ECS+proph. LMWH | | | 0/76 (0.0) | 1/76 (1.3) | not estimable | 0.08 (0.01-0.59) |
| | ECS+proph. UFH | | | 0/71 (0.0) | 2/71 (2.8) | not estimable | 0.17 (0.04-0.72) |
| | ECS+VKA | | | 0/71 (0.0) | 5/71 (7.0) | not estimable | 0.42 (0.16-1.12) |
| Marchiori *et al.*[††] | low-dose UFH | 30 | 6 | 6/30 (20.0) | 11/30 (36.7) | – | – |
| (2002) | high-dose UFH | | | 1/30 (3.3) | 8/30 (26.7) | 0.17 (0.02-1.3) | 0.73 (0.34-1.55) |
| Stenox[§§] | placebo | 8-10 | 3 | 5/112 (4.5) | 33/112 (29.5) | – | – |
| (2003) | proph. LMWH | | | 6/110 (5.5) | 13/110 (11.8) | 1.22 (0.38-3.89) | 0.40 (0.22-0.72) |
| | therap. LMWH | | | 4/106 (3.8) | 13/106 (12.3) | 0.85 (0.23-3.06) | 0.42 (0.23-0.75) |
| | NSAID | | | 4/99 (4.0) | 12/99 (12.1) | 0.91 (0.25-3.28) | 0.41 (0.23-0.75) |
| Lozano *et al.*[@] | surgery | 28 | 6 | 2/30 (6.7) | 1/30 (3.3) | not estimable | 0.33 (0.04-3.03) |
| (2003) | therap. LMWH | | | 0/30 (0.0) | 3/30 (10.0) | not estimable | – |

*VTE: venous thrombo-embolism; SVT, superficial vein thrombosis; NSAID: non-steroidal anti-inflammatory drug; LMWH: low-molecular-weight heparin; a: adjusted to bodyweight dose; f: fixed dose; ECS: elastic compression stockings; UFH: unfractionated heparin; Stenox, The Superficial Thrombophlebitis Treated by Enoxaparin Study Group. [†]RR is calculated by comparison to NSAID; [§]RR is calculated by comparison to ECS only; [††]RR is calculated by comparison to low-dose UFH, overall events after 6 months of follow-up; [§§]RR is calculated by comparison to placebo; [@]RR is calculated by comparison to therapeutic LMWH.*

day 7 one of the patients (2.7%) in the NSAID group, one (2.8%) in the fixed dose LMWH group and two (5.0%) in the adjusted dose LMWH group had extension of SVT. Whether these patients were treated with anticoagulant therapy based on these findings was not mentioned. After eight weeks, one patient had a recurrent thrombus and one patient a new thrombus in the superficial veins; both had been allocated to the fixed dose of LMWH treatment arm. The absolute event rate of this outcome was 2/36 (5.6%) (Table 2). No major bleeding or heparin-induced thrombocytopenia was observed during the course of this trial. There were several methodological drawbacks in this trial. First, the trial was open and the method of allocation was not described. Second, ultrasonography to assess the deep and superficial venous system for the presence of DVT, progression of SVT or recurrence of SVT was not performed by an assessor blinded to the treatment regimen.

The second trial by Belcaro *et al*. evaluated the effects of different treatment regimens (Table 2).[32] In this open study, patients with SVT in the presence of large varicose veins were included. Patients with DVT or SVT located in the saphenous vein with an extension towards the femoral vein were treated with anticoagulant therapy. After six months of follow-up, the incidence of DVT was 7.7% in the control group, as compared to 0% in the three groups treated with anticoagulants (RR not estimable). No new DVT occurred in the last three months of follow-up. The incidence of thrombus extension after six months varied between 1.3% and 16.7% (Table 2). Safety outcomes were not reported in this trial. Again, there were several methodological limitations in this trial. First, there was a high percentage of dropouts (i.e. 21%: 444 patients available for follow-up of the 562 included). Second, the trial was incompletely reported, making quality assessment difficult. Although the trial was described as being randomized, no details were given about the method of allocation; the dosages of LMWH and of subcutaneously injected UFH, as well as the intended INR range of the VKA group were not described; and the duration of treatment was not specified. Third, ultrasonography to assess the deep and superficial venous systems for presence of DVT, progression of SVT or recurrence of SVT was not performed by an assessor blinded to the treatment regimen.

The third open trial by Marchiori *et al*. was performed in patients with acute SVT of the great saphenous vein (Table 2).[33] Six patients in the low-dose heparin group (20.0%) developed VTE; four of

these episodes occurred during treatment. One patient in the high-dose heparin group (3.7%) developed VTE (compared to low-dose heparin: RR 0.17, 95% CI 0.02 to 1.30). Extension and/or recurrence of the SVT was seen in 11 patients (36.7%) in the low-dose heparin group; seven of these occurred during treatment. Eight patients (26.7%) had an extension and/or recurrence of SVT in the high-dose heparin group (compared to low-dose heparin: RR 0.73; 95% CI 0.34 to 1.55), of whom three (10.0%) during treatment. No death, major bleeding or heparin-induced thrombocytopenia was observed during the course of this trial. One of the limitations of this trial was the small number of patients (60). Also, the use of systemic and/or local anti-inflammatory drugs was allowed in this study, but no details were given.

The fourth randomized trial by the Stenox-group was a well designed, double blind study in which 436 patients were included and three different treatment regimens were compared with placebo (Table 2).[16] All patients had to wear elastic stockings. After ten days, the incidence of VTE tended to be lower in the treatment groups than in the placebo group, but these differences were not statistically significant (RR 0.26, 95% CI 0.03-2.24 for prophylactic LMWH, RR 0.26, 95% CI 0.03-2.33 for therapeutic LMWH, and RR 0.57, 95% CI 0.11-3.02 for NSAID). After three months, the trend in favor of the active treatment groups disappeared, suggesting a catch-up phenomenon. This effect was especially prominent in the first three weeks after cessation of treatment. After three months, the incidences of extension and/or recurrence of SVT in the groups treated with either dosage of LMWH or NSAID were lower than the 29.5% observed in the placebo group (RR 0.40, 95% CI 0.22 to 0.72 for prophylactic LMWH, RR 0.42, 95% CI 0.23 to 0.75 for therapeutic LMWH, and RR 0.41, 95% CI 0.23-0.75 for NSAID). Isolated recurrence of SVT or extension toward the saphenofemoral junction was observed in 56 patients directly after cessation of treatment by day 12; 21 patients were not treated for this extension. Of these, 5 (23.8%) experienced symptomatic VTE during follow-up, whereas none of the remaining 35 who were treated did so. No death, major bleeding or heparin-induced thrombocytopenia was observed during the course of this trial.

The fifth open, randomized trial by Lozano *et al.* evaluated two different treatments for great saphenous vein thrombosis.[34] All patients had to wear elastic compression stockings and acetaminophen was prescribed for pain. During the course of follow-up no VTE occurred in the patients treated with LMWH unlike in the patients who underwent surgical treatment, of whom two (6.7%) were diagnosed with PE. Recurrence of SVT was seen in one patient (3.3%) in the surgery group compared to three patients (10.0%) in the LMWH group (RR 0.33; 95% CI 0.04-3.03). No death or major bleeding was observed during the course of this trial. There were several methodological drawbacks in this trial. First of all, the trial was presented as randomized although the allocation method was not mentioned. Second, outcome assessment was not performed in a blinded manner. Third, no placebo group was used and the group of patients studied was rather small (60) (Table 2).

### Discussion

Three of the five studies included in our review were of low methodological quality, with unclear randomization methods, no placebo control group, unblinded outcome assessment or an unacceptably high drop-out rate.[31,32,34] One study was of intermediate methodological quality with its most important drawback being the lack of a placebo control group.[33] This study showed a trend in favor of treatment with high-dose compared to low-dose UFH for the prevention of VTE, but without statistical significance. This may have been due to a lack of power, since the number of patients studied was very small. Only one study was of good quality and showed a trend in favor of active treatment, i.e. use of a NSAID, prophylactic or therapeutic LMWH as compared to placebo for the outcomes of SVT extension and/or recurrence, but with a lack of longer-term benefit.[16] Although a short-term trend in favor of active treatment was seen with respect to VTE, this reduction did not reach statistical significance. However, this could be due to a lack of power given the moderate number of patients studied in each treatment arm. The catch-up phenomenon, i.e. disappearance of the favorable trend of active treatment after three months of follow-up, which was observed for VTE but not for SVT extension and/or recurrence, could be due to the short duration of treatment, since this effect was especially prominent in the first three weeks after cessation of treatment. This phenomenon has also been described for VTE.[35]

### Conclusions and recommendations

In conclusion, the absolute risk of VTE and SVT extension and/or recurrence in SVT is considerable. Compared to placebo, active treatment with LMWH or NSAID reduces the incidence of SVT extension or recurrence, but this could not be demonstrated with respect to the incidence of VTE at longer follow-up. Therefore, more randomized controlled trials that have variable durations of treatment are needed before any evidence-based recommendations can be made about the optimal treatment of SVT in order to prevent VTE.

What would be a reasonable approach to patients with SVT in clinical practice? With the present lack of solid evidence we would suggest treating patients with

at least intermediate doses of LMWH, schedule a follow-up appointment and instruct patients to report any symptoms of recurrence or DVT. Given the observation that 1 week of LMWH treatment is probably too short to prevent recurrences in the longer term, a treatment period of at least 4 weeks is suggested in the most recent ACCP guidelines.[36] Surgical treatment of SVT may be considered when varicose veins are involved.

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