

# PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

## International Consensus Statement 2013 Guidelines According to Scientific Evidence

*Developed under the auspices of the:*

Cardiovascular Disease Educational and Research Trust (UK)

European Venous Forum

North American Thrombosis Forum

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Union Internationale du Phlebologie

# Superficial Vein Thrombosis

## Chapter 21

# General Considerations

## Incidence

- **Incidence of superficial vein (SVT) in the general population ranges from 3% to 11%<sup>1-4</sup>**
  - ▶ SVT is more common (50-70%) in women<sup>1, 5-14</sup>
  - ▶ Prevalence is 0.05 per 1000 men per year and 0.31 per 1000 women per year during the third decade of life<sup>1-4</sup>
  - ▶ Increases to 1.8 per 1000 men per year and 2.2 per 1000 women per year during the eighth decade of life<sup>1-4</sup>
  - ▶ Mean age of presentation is 60 years<sup>1, 5-8,9,15,16</sup> and the older the patient, the fewer risk factors are present<sup>15, 17</sup>

1. Leon L, et al. Eur J Vasc Endovasc Surg. 2005; 29:10-7.

2. Schonauer V, et al. J Vasc Surg. 2003; 37:834-8.

3. Coon WW, et al. Circulation. 1973; 48:839-46.

4. Decousus H, et al. Thromb Res. 2011; 127 Suppl 3:S81-5.

5. Decousus H, et al. Curr Opin Pulm Med. 2003; 9:393-7.

6. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.

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

8. Husni EA, et al. Surgery. 1982; 91:70-4.

9. Martinelli I, et al. Thromb Haemost. 1999; 82:1215-7.

10. Gillet JL, et al. J Mal Vasc. 2001; 26:16-22.

11. Unno N, et al. Surg Today. 2002; 32:397-401.

12. Lofgren EP, et al. Surgery. 1981; 90:49-54.

13. Marchiori A, et al. Semin Thromb Hemost. 2006; 32:737-43.

14. Binder B, et al. Arch Dermatol. 2009; 145:753-7.

15. Chengelis DL, et al. J Vasc Surg. 1996; 24:745-9.

16. Ascer E, et al. J Vasc Surg. 1995; 22:616-21.

17. Rosendaal FR. Thromb Haemost. 1997; 78:1-6.

# General Considerations

## Vein Involvement

- **The great saphenous system is involved in 60-80% of cases of SVT the small saphenous system in 10-20%<sup>1-4</sup>**
- **Bilateral SVT is reported in 5-10% of patients<sup>1, 5-8</sup>**
- **Development of SVT in patients with varicose veins rages from 4-59%,<sup>1,6-9</sup>**
  - ▶ Confined more frequently to varicose tributaries rather than the saphenous trunks.<sup>1,9</sup>

1. Leon L, et al. Eur J Vasc Endovasc Surg. 2005; 29:10-7.
2. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.
3. Decousus H, et al. J Thromb Haemost. 2005; 3:1149-51.
4. Lutter KS, et al. Surgery. 1991; 110:42-6.
5. Decousus H, et al. Curr Opin Pulm Med. 2003; 9:393-7.
6. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.
7. Lutter KS, et al. Surgery. 1991; 110:42-6.
8. Husni EA, et al. Surgery. 1982; 91:70-4.
9. Lofgren EP, et al. Surgery. 1981; 90:49-54.

# General Considerations

## Vein Involvement

- **SVT of the great saphenous vein above knee is associated with 17-19% incidence of DVT whereas SVT confined to the below knee segment has an incidence of associated only in 4-5% of patients<sup>1-3</sup>**
- **SVT may coexist with DVT in 6-53% of patients presenting with SVT<sup>4-20</sup>**
  - ▶ Extension from great saphenous vein to the femoral vein is common<sup>9</sup>
- **DVT may complicate isolated SVT in a short term<sup>4,5,21,22</sup>**

1. Chengelis DL, et al. J Vasc Surg. 1996; 24:745-9.
2. Quenet S, et al. J Vasc Surg. 2003; 38:944-9.
3. Bergqvist D, et al. Br Med J (Clin Res Ed). 1986; 292:658-9.
4. Decousus H, et al. Thromb Res. 2011; 127 Suppl 3:S81-5.
5. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.
6. Husni EA, et al. Surgery. 1982; 91:70-4.
7. Unno N, et al. Surg Today. 2002; 32:397-401.
8. Lofgren EP, et al. Surgery. 1981; 90:49-54.
9. Lutter KS, et al. Surgery. 1991; 110:42-6.
10. Plate G, et al. Acta Chir Scand. 1985; 151:241-4.
11. Skillman JJ, et al. J Vasc Surg. 1990; 11:818-23; discussion 23-4.

12. Lohr JM, et al. Am J Surg. 1992; 164:269-75.
13. Jorgensen JO, et al. J Vasc Surg. 1993; 18:70-3.
14. Blumenberg RM, et al. J Vasc Surg. 1998; 27:338-43.
15. Bounameaux H, et al. Arch Intern Med. 1997; 157:1822-4.
16. Sobreira ML, et al. Int Angiol. 2009; 28:400-8.
17. Galanaud JP, et al. Thromb Haemost. 2011; 105:31-9.
18. Pulliam CW, et al. Ann Vasc Surg. 1991; 5:190-5.
19. Proutjos P, et al. Int Angiol. 1991; 10:63-5.
20. Murgia AP, et al. Int Angiol. 1999; 18:343-7.
21. Decousus H, et al. N Engl J Med. 2010; 363:1222-32.
22. Dewar C, et al. Emerg Med J. 2010; 27:758-61.

# General Considerations

## Risk Factors

- **Obesity, age and protein-S deficiency are factors associated with SVT episodes in patients with varicose veins<sup>1</sup>**
- **SVT in patients without varicose veins is found in 5-10% of all patients<sup>2-4</sup>**

1. Karathanos C, et al. Eur J Vasc Endovasc Surg. 2012; 43:355-8.
2. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.
3. Decousus H, et al. N Engl J Med. 2010; 363:1222-32.
4. Gillet JL, et al. J Mal Vasc. 2004; 29:263-72.

# General Considerations

## Etiology

- **Autoimmune disease (Behçet's, Buerger's and Mondor's disease)<sup>1,2</sup>**
- **Malignancy<sup>1-4</sup>**
- **Thrombophilia,<sup>1,2,6,7-17</sup>**
- **Mechanical or chemical trauma or injury (venous infusion, catheter introduction)<sup>18</sup>**
- **Radiation injury<sup>18</sup>**
- **Bacterial or fungal infections<sup>18</sup>**

1. Decousus H, et al. *Thromb Res.* 2011; 127 Suppl 3:S81-5.

2. Decousus H, et al. *Curr Opin Pulm Med.* 2003; 9:393-7.

3. Barrellier MT. *Phlebologie.* 1993; 46:633-9.

4. Naschitz JE, et al. *Angiology.* 2003; 54:11-7.

5. Schonauer V, et al. *J Vasc Surg.* 2003; 37:834-8.

6. Hanson JN, et al. *J Vasc Surg.* 1998; 27:677-80.

7. Martinelli I, et al. *Thromb Haemost.* 1999; 82:1215-7.

8. de Moerloose P, et al. *Thromb Haemost.* 1998; 80:239-41.

9. Samlaska CP, et al. *J Am Acad Dermatol.* 1990; 22:975-89.

10. de Godoy JM, et al. *Angiology.* 2001; 52:127-9.

11. Engesser L, et al. *Ann Intern Med.* 1987; 106:677-82.

12. Pabinger I, et al. *Arterioscler Thromb Vasc Biol.* 1996; 16:742-8.

13. de Godoy JM, et al. *Clin Appl Thromb Hemost.* 2003; 9:61-2.

14. Gorty S, et al. *Vasc Med.* 2004; 9:1-6.

15. Caprini JA, et al. *Eur J Vasc Endovasc Surg.* 2005; 30:550-5.

16. Leon LR, Jr., et al. *Perspect Vasc Surg Endovasc Ther.* 2005; 17:43.

17. Milio G, et al. *Thromb Res.* 2008; 123:194-9.

18. Kalodiki E, et al. *Int Angiol.* 2012; (in press).

# General Considerations

## Risk Factors

- **Risk factors are similar to those for DVT<sup>1,2</sup>**
  - ▶ Previous thromboembolic events
  - ▶ Long-haul flights<sup>3,4</sup>
  - ▶ Pregnancy<sup>5,6</sup>
  - ▶ Oral contraceptives
  - ▶ Hormone replacement therapy
  - ▶ Immobilization<sup>7,8</sup>
  - ▶ Obesity
  - ▶ Recent surgery<sup>7</sup>
  - ▶ Trauma<sup>7,8</sup>
  - ▶ Sclerotherapy<sup>9</sup>
- **Obesity is associated with increased prothrombotic factors<sup>10</sup> and an independent risk factor for VTE<sup>11-13</sup> and SVT<sup>2,14,15</sup>**

1. Martinelli I, et al. *Thromb Haemost.* 1999; 82:1215-7.

2. Quenet S, et al. *J Vasc Surg.* 2003; 38:944-9.

3. Scurr JH, et al. *Lancet.* 2001; 357:1485-9.

4. Clarke M, et al. *Cochrane Database Syst Rev.* 2006; CD004002.

5. James KV, et al. *Cardiovasc Surg.* 1996; 4:777-82.

6. McColl MD, et al. *Thromb Haemost.* 1998; 79:741-2.

7. Gillet JL, et al. *J Mal Vasc.* 2001; 26:16-22.

8. Samlaska CP, et al. *J Am Acad Dermatol.* 1990; 23:1-18.

9. Ikeda M, et al. *Thromb Res.* 1996; 82:87-95.

10. Rosito GA, et al. *Thromb Haemost.* 2004; 91:683-9.

11. Stein PD, et al. *Am J Med.* 2005; 118:978-80.

12. Darvall KA, et al. *Eur J Vasc Endovasc Surg.* 2007; 33:223-33.

13. Hansson PO, et al. *Arch Intern Med.* 1999; 159:1886-90.

14. Leon L, et al. *Eur J Vasc Endovasc Surg.* 2005; 29:10-7.

15. de Moerloose P, et al. *Thromb Haemost.* 1998; 80:239-41.



# General Considerations

## Association with VTE

- **SVT is a risk factor for the development and recurrence of DVT<sup>1-5</sup>**
- **PE has been observed in 1.5-33% of SVT patients<sup>2,3,6-12</sup>**
  - ▶ PE was reported in 18% of patients when the thrombotic process was in the GSV above the knee and 4% when in the SSV<sup>8</sup>
  - ▶ PE may complicate “isolated” SVT in the short term (3-4 months after the episode of SVT)<sup>3,6,13</sup>
  - ▶ SVT is a risk factor for development and recurrent PE<sup>1-5</sup>
  - ▶ It is unclear whether PE associated with SVT arises from extension to deep veins or from thrombus that is only in the superficial venous system<sup>1</sup>

1. Leon L, et al. Eur J Vasc Endovasc Surg. 2005; 29:10-7.
2. Decousus H, et al. Thromb Res. 2011; 127 Suppl 3:S81-5.
3. Decousus H, et al. Ann Intern Med. 2010; 152:218-24.
4. Decousus H, et al. J Thromb Haemost. 2005; 3:1149-51.
5. Samama MM, et al. Haematologica. 2003; 88:1410-21.
6. Decousus H, et al. N Engl J Med. 2010; 363:1222-32.

7. Unno N, et al. Surg Today. 2002; 32:397-401.
8. Lutter KS, et al. Surgery. 1991; 110:42-6.
9. Blumenberg RM, et al. J Vasc Surg. 1998; 27:338-43.
10. Sobreira ML, et al. Int Angiol. 2009; 28:400-8.
11. Gjores JE. Angiology. 1962; 13:241-3.
12. Verlato F, et al. J Vasc Surg. 1999; 30:1113-5.
13. Quenet S, et al. J Vasc Surg. 2003; 38:944-9.

# General Considerations

## Link with Pregnancy

- **The link between SVT and pregnancy is unclear and the prevalence is very low (0.05-0.1%)<sup>1-7</sup>**
  - ▶ Possibly underestimated secondary to the lack of symptoms<sup>3,4</sup>

1. Leon L, et al. Eur J Vasc Endovasc Surg. 2005; 29:10-7.
2. Martinelli I, et al. Thromb Haemost. 1999; 82:1215-7.
3. James KV, et al. Cardiovasc Surg. 1996; 4:777-82.
4. McColl MD, et al. Thromb Haemost. 1998; 79:741-2.
5. Kupelian AS, et al. Arch Gynecol Obstet. 2007; 275:215-7.
6. Aaro LA, et al. Am J Obstet Gynecol. 1967; 97:514-8.
7. Cook G, et al. Br J Haematol. 1994; 87:873-5.

# General Considerations

## Presentation and Diagnosis

- **SVT presents with local pain, warmth, erythema, swelling and the SVT becomes solid like a cord<sup>1-4</sup>**
- **Diagnosis should include Duplex ultrasound for confirmation, estimation of thrombus extent, exclusion of deep venous thrombosis and for follow-up<sup>2,5-18</sup>**
- **The term superficial thrombophlebitis should be discouraged because inflammation and infection is not the primary pathology<sup>19</sup>**
  - ▶ Called SVT to avoid unnecessary administration of antibiotics

1. Leon L, et al. Eur J Vasc Endovasc Surg. 2005; 29:10-7.
2. Decousus H, et al. Curr Opin Pulm Med. 2003; 9:393-7.
3. Kalodiki E, et al. Angiology. 2002; 53:659-63.
4. Pabinger I, et al. Arterioscler Thromb Vasc Biol. 1996; 16:742-8.
5. Decousus H, et al. Thromb Res. 2011; 127 Suppl 3:S81-5.
6. Ascer E, et al. J Vasc Surg. 1995; 22:616-21.
7. Chengelis DL, et al. J Vasc Surg. 1996; 24:745-9.
8. Marchiori A, et al. Semin Thromb Hemost. 2006; 32:737-43.
9. Lutter KS, et al. Surgery. 1991; 110:42-6.

10. Barrellier MT. Phlebologie. 1993; 46:633-9.
11. Skillman JJ, et al. J Vasc Surg. 1990; 11:818-23; discussion 23-4.
12. Lohr JM, et al. Am J Surg. 1992; 164:269-75.
13. Jorgensen JO, et al. J Vasc Surg. 1993; 18:70-3.
14. Blumenberg RM, et al. J Vasc Surg. 1998; 27:338-43.
15. Bounameaux H, et al. Arch Intern Med. 1997; 157:1822-4.
16. Pulliam CW, et al. Ann Vasc Surg. 1991; 5:190-5.
17. Proutjos P, et al. Int Angiol. 1991; 10:63-5.
18. Denzel C, et al. Zentralbl Chir. 2001; 126:374-8.
19. Kalodiki E, et al. Int Angiol. 2012; (in press).

# General Considerations

## Treatment

- **Variations in treatment**
- **A cross-sectional and prospective epidemiologic cohort study (POST) in France, a total of 634 patients had isolated SVT at inclusion<sup>1</sup>**
  - ▶ Information regarding treatment was available for 597 patients
  - ▶ 540 (90.5%) received one or more anticoagulant drugs either at therapeutic doses 374 (62.9%) or at prophylactic doses 216 (36.7%)
  - ▶ 584 (97.7%) had elastic stockings compression stockings
  - ▶ 278 (47.2%) received topical NSAIDs
  - ▶ 48 (8.2%) received NSAIDS
  - ▶ 60 patients (10.2%) had venous surgery (stripping or ligation)

# General Considerations

## Treatment with LMWH or VKA

- **Randomized, open trial (N=562) patients with SVT associated with varicose veins has shown that UFH, LMWH or VKA had equal efficacy<sup>1</sup>**
  - ▶ LMWH and VKA were superior to elastic compression or flush ligation combined with elastic compression for SVT extension at three months<sup>1</sup>

# General Considerations

## Treatment with NSAID

- **A RCT with 427 patients compared LMWH (enoxaparin 40 mg and 1.5 mg/kg) with a NSAID (tenoxicam) and placebo for 8-12 days<sup>1</sup>**
  - ▶ Rates of DVT and SVT as detected by ultrasonography at 12 days was 30.6% in the placebo, 14.9% in the tenoxicam, 6.9% in the enoxaparin 1.5mg/kg and 8.3% in the enoxaparin 40 mg ( $P < 0.01$ )
- **Another open randomized trial (N=117) demonstrated LMWH (nadroparin) was superior to NSAID in reducing symptoms at six days ( $P < 0.001$ ) and eight weeks ( $P=0.007$ )<sup>2</sup>**

1. Decousus H, et al. Arch Intern Med. 2003; 163:1657-63.

2. Titon JP, et al. Ann Cardiol Angeiol (Paris). 1994; 43:160-6.

# General Considerations

## Treatment with Unfractionated Heparin

- **High doses of UFH twice daily (12,500 IU for one week followed by 10,000 IU for three weeks) were superior to prophylactic doses (5,000) twice daily in 60 randomized patients<sup>1</sup>**
  - ▶ During the six month follow-up the rate of asymptomatic involvement of the deep veins and/or symptomatic VTE was reduced from 20% in the prophylactic dose to 3.3% in the high dose group (P = 0.05)
- **When therapeutic doses of nadroparin were compared with prophylactic doses, progression or VTE occurred in 7.2% and 8.6% of patients respectively<sup>2</sup>**

1. Marchiori A, et al. Haematologica. 2002; 87:523-7.

2. Prandoni P, et al. J Thromb Haemost. 2005; 3:1152-7.

# General Considerations

## Review of Trials

- **A systematic review that included 5 randomized controlled trials, pooling of the data was not possible due to their heterogeneity<sup>1</sup>**
  - ▶ 3 of the studies had serious methodological drawbacks limiting the clinical applicability of their results
  - ▶ In the remaining 2 studies:
    - A non-significant trend in favor of high-dose UFH to low-dose UFH for prevention of VTE was observed
    - A non-significant trend in favor of short-term treatment with LMWH or NSAID compared to placebo VTE was observed in the other



# General Considerations

## Review of Trials

- **A systematic review of 24 trials (N=2469) of SVT treatment identified most studies had poor methodological quality<sup>1</sup>**
  - ▶ Treatments included LMWH, NSAID, topical treatment, surgery and compression stockings
  - ▶ The investigators concluded that LMWH and NSAID significantly reduced the incidence of extension or recurrence of SVT by ~70% compared with placebo
  - ▶ Topical treatments improved local symptoms but there was not any report on the progression to DVT
  - ▶ Surgical treatment combined with elastic stockings was associated with lower rate of VTE and progression of SVT compared with elastic stockings alone
  - ▶ Authors recommended an intermediate dose of LMWH for at least 1 month and indicated further research was needed to assess the role of NSAID and LMWH, the optimal doses, and duration of treatment, and whether combination therapy may be more effective than single treatment

# General Considerations

## Review of Trials

- **A small RCT (N=72) compared LMWH (dalteparin) with a NSAID n(ibuprofen) for 14 days<sup>1</sup>**
  - ▶ Extension of the thrombosis in four (11%) patients in the dalteparin group and in none in the ibuprofen group (P = 0.05)
  - ▶ Significant reduction in pain in both groups compared to baseline
  - ▶ No difference in the reduction of pain between the groups during the treatment period or at 14 days
  - ▶ No statistical difference in the extension of thrombosis at three months after treatment was stopped

# General Considerations

## Review of Trials

- **An international RCT of 3002 patients compared fondaparinux subcutaneously 2.5mg once daily for 45 days with placebo<sup>1</sup>**
  - ▶ Eligible for inclusion were hospitalized or non-hospitalized patients 18 years or older with acute symptomatic lower limb SVT at least five cm long as confirmed by compression ultrasonography
  - ▶ Primary efficacy outcome was death from any cause or symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of DVT
  - ▶ At day 47, the primary outcome occurred in 0.9% of patients in the fondaparinux group and 5.9% in the placebo group ( $P < 0.001$ )
  - ▶ Similar risk reductions were observed at day 77
  - ▶ No difference was observed in major bleeding between the groups

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

# General Considerations

## Review of Trials

- **Review of 6 studies comparing surgery to anticoagulation showed similar rates of SVT progression, but the incidence of VTE and complications was higher with surgery<sup>1</sup>**
- **Surgical treatment with elastic stockings was associated with lower VT rate and SVT progression compared to elastic stockings alone<sup>2</sup>**
- **No difference was seen between surgery and enoxaparin for four weeks<sup>3</sup>**

1. Sullivan V, et al. J Am Coll Surg. 2001; 193:556-62.
2. Bergqvist D, et al. Ann Chir Gynaecol. 1990; 79:92-6.
3. Lozano FS, et al. Vasc Endovascular Surg. 2003; 37:415-20.

# General Considerations

## Review of Trials

- **Antibiotics have no role in management of SVT except in cases secondary to indwelling intravenous catheters<sup>1,2</sup>**
- **Hirudoids have some effect in alleviating pain and local inflammatory signs and a few topical agents (hirudoid cream, piroxicam cream, piroxicam patch) are available<sup>3</sup>**
- **Local application of heparinoid cream was better than placebo<sup>4,5</sup>**
- **Local application of heparin was reported to have effects on symptoms comparable to LMWH<sup>6</sup>**
- **Elastic stockings are traditionally used if tolerated as an adjunctive treatment together with anticoagulation<sup>7,8</sup>**

1. Kalodiki E, et al. *Int Angiol*. 2012; (in press).

2. Hafner CD, et al. *Surgery*. 1964; 55:201-6.

3. Bergqvist D, et al. *Ann Chir Gynaecol*. 1990; 79:92-6.

4. Mehta PP, et al. *Br Med J*. 1975; 3:614-6.

5. Vilardell M, et al. *Eur J Clin Pharmacol*. 1999; 54:917-21.

6. Katzenschlager R, et al. *Journal fur Kardiologie*. 2003; 10:375-8.

7. Decousus H, et al. *Curr Opin Pulm Med*. 2003; 9:393-7.

8. Gorty S, et al. *Vasc Med*. 2004; 9:1-6.

# Recommendations

## Superficial Vein Thrombosis

- **All patients with SVT should have bilateral duplex scanning to exclude DVT**
  - ▶ Level of evidence: High
- **LMWH in intermediate doses for at least one month is recommended**
  - ▶ Level of evidence: Moderate
- **Fondaparinux 2.5 mg daily for at least four weeks is an effective treatment**
  - ▶ Level of evidence: High
- **Surgery is not better than LMWHs**
  - ▶ Level of evidence: Low

# Recommendations

## Superficial Vein Thrombosis

- **When thrombus is close to saphenofemoral or saphenopopliteal junctions LMWHs in therapeutic doses or surgery (ligation) are both acceptable options depending on the patient's characteristics and the treating physician's preference**
  - ▶ Level of evidence: Low
- **For isolated SVT at the below knee segment confined to varicosities, local application of heparinoids, NSAIDs and elastic stockings is an acceptable treatment option**
  - ▶ Level of evidence: Low