

# PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

## International Consensus Statement 2013 Guidelines According to Scientific Evidence

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Cardiovascular Disease Educational and Research Trust (UK)

European Venous Forum

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# Prevention of Post-Thrombotic Syndrome

## Chapter 22

# General Considerations

## Post-thrombotic Syndrome

- **~30-50% of patients with DVT develop the post-thrombotic syndrome (PTS)<sup>1</sup>**
  - ▶ PTS develops despite appropriate anticoagulation therapy
  - ▶ Established PTS is a significant cause of chronic incapacity<sup>2-5</sup>
- **PTS is the result of venous hypertension from reflux in veins with damaged valves, outflow obstruction or a combination of both<sup>6</sup>**
- **Venous hypertension is associated with chronic inflammation<sup>7</sup>**
  - ▶ Excessive capillary leakage
  - ▶ Skin nutrition becomes impaired
  - ▶ Development of skin ulceration

1. Prandoni P, et al. Haematologica 1997; 82:423-8.

2. Delis KT, et al. Ann Surg 2004; 239:118-26.

3. Kahn SR, et al. Ann Intern Med 2008; 149:698-707.

4. O'Donnell TF, et al. J Surg Res 1977; 22:483-8.

5. Monreal M, et al. J Intern Med 1993; 233:233-8.

6. Shull KC, et al. Arch Surg 1979; 114:1304-6.

7. Bergan JJ, et al. N Engl J Med 2006; 355:488-98.

# General Considerations

## Signs and Symptoms of PTS

- **Signs and symptoms of PTS may vary<sup>1</sup>**
  - ▶ Venous ulcer is the most predictive clinical finding<sup>1,2</sup>
  - ▶ Develop as early as 3 months of DVT<sup>1,2</sup>
- **Factors associated with development of PTS include<sup>3-7</sup>**
  - ▶ Iliofemoral DVT
  - ▶ Chronic iliofemoral vein obstruction
  - ▶ Increased BMI
  - ▶ Recurrent DVT
- **Elevated inflammatory biomarkers (IL-6, ICAM-1, CRP) are associated with increased rates of PTS post-DVT<sup>8,9</sup>**

1. Rodger MA, et al. Thromb Haemost 2008; 100:164-6.

2. Kahn SR, et al. Ann Intern Med 2008; 149:698-707.

3. Delis KT, et al. Ann Surg 2004; 239:118-26.

4. Neglen P, et al. J Vasc Surg 2007; 46:979-990.

5. Meissner MH, et al. J Vasc Surg 2007; 46 Suppl S:68S-83S.

6. Prandoni P, Kahn SR. Br J Haematol 2009; 145:286-95.

7. van Dongen CJ, et al. J Thromb Haemost 2005; 3:939-42.

8. Shbaklo H, et al. Thromb Haemost 2009; 101:505-12.

9. Roumen-Klappe EM, et al. J Thromb Haemost 2009; 7:582-7.

# Prevention of PTS

## Prevention of Primary and Secondary DVT

- **Prevention of DVT should reduce the prevalence of PTS in the general population<sup>1</sup>**
- **Guidelines aimed to reduce PTS and leg ulcers by 50% by year 2020 have been published<sup>2</sup>**

1. Kahn SR, et al. Ann Intern Med 2008; 149:698-707.

2. Henke P, et al. J Vasc Surg 2010; 52:37S-38S.

# Review of Evidence

## Graduated Elastic Compression and PTS

- **Effective graduated elastic compression has been shown to reduce venous hypertension, edema and minimize the damage to the microcirculation<sup>1,2</sup>**
  - ▶ Four RCTs (745 patients) have demonstrated that elastic compression for 2 years in patients with proximal DVT reduced the incidence of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62)<sup>3-6</sup>
  - ▶ Treatment of DVT with LMWH combined with early ambulation and elastic compression further prevents the PTS<sup>7,8</sup>

1. Pierson S, et al. JAMA 1983; 249:242-3.

2. Musani MH, et al. Am J Med 2010; 123:735-40.

3. Prandoni P, et al. Ann Intern Med 2004; 141:249-56.

4. Ginsberg JS, et al. Arch Intern Med 2001; 161:2105-9.

5. Brandjes DP, et al. Lancet 1997; 349:759-62.

6. Aschwanden M, et al. J Vasc Surg 2008; 47:1015-21.

7. Partsch H, et al. J Vasc Surg 2000; 32:861-9.

8. Partsch H, et al. Int Angiol 2004; 23:206-12.

# Review of Evidence

## Early Surgical Thrombectomy and PTS

- **Early surgical thrombectomy for iliofemoral DVT may increase iliac vein patency versus anticoagulation therapy alone (67% vs 34%; RR 1.92; 95% CI 1.06 to 3.51)<sup>1,2</sup>**
  - ▶ Incidence of PTS decrease from 93% with anticoagulation only to 58% with thrombectomy (RR 0.63; 95% CI 0.44 to 0.90)<sup>1,2</sup>
- **Catheter directed thrombolysis increased vein patency and reduced PTS compared with conventional anticoagulation therapy in a limited number of patients<sup>3-6</sup>**

1. Plate G, et al. Eur J Vasc Endovasc Surg 1997; 14:367-74.

2. Comerota AJ, Gale SS. J Vasc Surg 2006; 43:185-91.

# Review of Evidence

## Catheter Directed Thrombolysis and PTS

- **Catheter directed thrombolysis increases vein patency and reduces PTS<sup>1-7</sup>**

- ▶ Two RCTs (138 patients) demonstrated a patency rate of 70% in the CDT group and 33% in the standard anticoagulation therapy group (RR 0.48; 95% CI 0.33 to 0.70)<sup>5,6</sup>
- ▶ Another RCT (209 patients) showed iliofemoral patency rates at 6 months of 64% with CDT versus 47% with conventional treatment (RR for patency 1.42; 95% CI 1.09 to 1.85)<sup>7</sup>
  - At 24 months, PTS developed in 41% of patients in the CDT group and 56% of patients with conventional treatment (RR 0.74; 95% CI 0.55 to 1.00; P=0.047)

1. AbuRahma AF, et al. Ann Surg 2001; 233:752-60.

2. Baekgaard N, et al. Eur J Vasc Endovasc Surg 2010; 39:112-7.

3. Comerota AJ. Phlebology 2001; 15:149-55.

4. Markevicius N, et al. Phlebology 2004; 19:148-9.

5. Elsharawy M, Elzayat E. Eur J Vasc Endovasc Surg 2002; 24:209-14

6. Enden T, et al. J Thromb Haemost 2009; 7:1268-75.

7. Enden T, et al. Lancet 2012; 379:31-8.



# Review of Evidence

## Percutaneous Endovascular Venoplasty and Stenting

- **Observational studies suggest percutaneous endovascular venoplasty and stenting to relieve chronic venous obstruction may alleviate PTS<sup>1,2</sup>**
- **In the largest series published<sup>1</sup>**
  - ▶ At 72 months, primary, assisted-primary, and secondary cumulative patency rates were 79%, 100%, and 100% in non-thrombotic disease and 57%, 80%, and 86% in thrombotic disease
  - ▶ Severe leg pain (VAS >5) and leg swelling (grade 3) decreased from 54% and 44% pre-stent to 11% and 18% post-stent
  - ▶ At 5 years, cumulative rates of complete relief of pain and swelling were 62% and 32% and ulcer healing was 58%

1. Neglen P, et al. J Vasc Surg 2007; 46:979-990.

2. Neglen P, Raju S. J Vasc Surg 2002; 35:694-700.

# Review of Evidence

## Long-Term LMWH Therapy and PTS

- **Studies have demonstrated that long-term LMWH produces improved recanalization<sup>1-6</sup>**
- **Meta-analysis of 5 studies reported improved recanalization and a reduced risk ratio of 0.66 (95% CI 0.57 to 0.77; P < 0.0001) in favor of long-term LMWH<sup>7</sup>**
- **Pooled analysis of studies yielded an 87% risk reduction with LMWH in the incidence of venous ulcers (P=0.019)<sup>8-9</sup>**

1. Das SK, et al. World J Surg 1996; 20:521-6; discussion 526-7.

2. Romera A, et al. Eur J Vasc Endovasc Surg 2009; 37:349-56.

3. Daskalopoulos ME, et al. Eur J Vasc Endovasc Surg 2007; 34:353-4.

4. Gonzalez-Fajardo JA, et al. J Vasc Surg 1999; 30:283-92.

5. Lopez-Beret P, et al. J Vasc Surg 2001; 33:77-90.

6. Kakkar VV, et al. Thromb Haemost 2003; 89:674-80.

7. Hull RD, et al. Am J Med 2011; 124:756-65.

8. Hull RD, et al. Am J Med 2009; 122:762-769 e3.

9. Daskalopoulos ME, et al. Eur J Vasc Endovasc Surg 2005; 29:638-50.

# Recommendations

## Prevention of Post-Thrombotic Syndrome

- **Early thrombus removal using CDT or pharmacomechanical thrombolysis may be used in expert centers in selected patients with iliofemoral DVT**
  - ▶ Level of evidence: Low
- **If thrombolysis is contraindicated, surgical thrombectomy could be used in expert centers**
  - ▶ Level of evidence: Low
- **Angioplasty and stenting of a proximal stenosis along with early thrombus removal may be required**
  - ▶ Level of evidence: Low

# Recommendations

## Prevention of Post-Thrombotic Syndrome

- **Although conventional anticoagulation therapy is based on a high level of evidence in terms of VTE recurrence, prolonged therapy with LMWH in patients with proximal DVT is preferable in terms of PTS prevention**
  - ▶ Level of evidence: Moderate
- **In patients with proximal DVT, graduated elastic compression stockings for at least two years in addition to appropriate anticoagulation are recommended**
  - ▶ Level of evidence: High