CHAPTER 8

THE POST-THROMBOTIC SYNDROME

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Abstract

One of every three patients with deep-vein thrombosis of the lower extremities will develop, within 5 years, post-thrombotic sequelae that vary from minor signs to severe manifestations such as chronic pain, intractable oedema, and leg ulceration. The post-thrombotic syndrome (PTS) develops as a result of the combination of venous hypertension due to persistent outflow obstruction and/or valvular incompetence, with abnormal microvasculature or lymphatic function. Among factors potentially related to the development of PTS, recurrent ipsilateral thrombosis plays a major role. Whether the extent and the location of the initial thrombosis are associated with the development of PTS is still controversial. The diagnosis of PTS can be accepted on clinical grounds for patients with a history of venous thrombosis. The combination of a standardised clinical evaluation with the results of compression ultrasonography and Doppler ultrasound helps diagnose or exclude a previous proximal-vein thrombosis. Prevention of recurrent thrombosis and use of compression elastic stockings are the cornerstones of PTS prevention. The management of this condition is demanding and often frustrating. Although several surgical procedures have been tested, conservative treatment is largely preferable, as more than 50% of patients either remain stable or improve during long-term follow-up, if carefully supervised and instructed to wear proper elastic stockings. Clinical presentation helps predict the prognosis, being the outcome of patients who refer with initially severe manifestations more favourable than that of patients whose symptoms progressively deteriorate over time.

Incidence

At least one of every three patients with deep-vein thrombosis (DVT) of the
lower extremities will develop, within 5 years, (severe) post-thrombotic sequelae. These sequelae vary from minor signs (i.e., stasis pigmentation, venous ectasia, slight pain and swelling) to severe manifestations such as chronic pain, intractable oedema, and leg ulcer. The established post-thrombotic syndrome (PTS) remains a significant cause of chronic ill health, with considerable socio-economic consequences for both the patient and the health care services.

The precise incidence of the PTS following confirmed venous thrombosis is still controversial, as the rate of post-thrombotic sequelae in the published studies has varied between 20% and 100%.\(^2\)\(^3\) In the earlier studies, an impressive rate of severe PTS complications was reported (50 to 100% of the patients within 4 to 10 years after the qualifying thrombotic episode).\(^2\)\(^5\) This rate sharply decreased in the studies performed in the last 20 years,\(^6\)\(^2\)\(^3\) most likely as the result of an improved diagnostic and therapeutic approach to patients with DVT. However, owing to large differences between studies in terms of design, definition of PTS, sample size, and length of follow-up, the reported incidence of both overall and severe PTS still show considerable variability (Table 1). Indeed, most studies have been limited to small or retrospective series of patients, with a high potential for bias due to either the selection of patients with extensive thrombotic disease or to failure to distinguish post-thrombotic sequelae from recurrent vein thrombosis. Recently, the results of a prospective randomised Dutch study on the prevention of PTS have become available.\(^1\)\(^8\) One hundred and ninety-four consecutive patients with confirmed proximal-vein thrombosis were allocated to wear or not elastic compression stockings. A scoring system was used to classify patients in three categories: no, mild-to-moderate, and severe PTS. After a median follow-up of 76 months, mild-to-moderate PTS occurred in 19 (20%) and severe PTS in 11 (11.5%) of the 96 patients with stockings, while this occurred in 46 (47%) and 23 (23.5%) of the 98 patients without stockings, respectively (p<0.001). In both groups, most of the cases of PTS developed within 24 months from the thrombotic event. The initial extent of DVT on venography was not related to the development of PTS.

The long-term incidence of PTS was determined in a cohort of 355 consecutive symptomatic patients with a first episode of venography proven DVT.\(^1\)\(^9\) All patients were treated with full-dose unfractionated or low-molecular-weight heparin followed by at least three months of oral anticoagulation and were instructed to wear compression elastic stockings as soon as possible after hospital discharge for at least 2 years. At each follow-up visit, the presence and severity of post-thrombotic signs and symptoms was scored using a standardised scale
Table 1- Prevalence of post thrombotic syndrome in a series of published trials.

<table>
<thead>
<tr>
<th>First author</th>
<th>Design</th>
<th>Sample †</th>
<th>Diagnosis ‡</th>
<th>Follow-up §</th>
<th>Stockings ¶</th>
<th>Overall</th>
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<th>Ulcer</th>
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<tr>
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<td>PF</td>
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<td>7-8</td>
<td>nr</td>
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<td>Ph</td>
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<td>Prandoni 1996</td>
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<td>355(100)</td>
<td>84(29)**</td>
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<td>96</td>
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<td>Biguzzi 1998</td>
<td>RE</td>
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<td>Ph/Dx</td>
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<td>38(74)</td>
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<td>nr</td>
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<td>Masuda 1998</td>
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<td>Cfd</td>
<td>3</td>
<td>nr</td>
<td>13(57)</td>
<td>1(5)</td>
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<td>McLaффerty 1998</td>
<td>RE</td>
<td>37</td>
<td>Cfd</td>
<td>3</td>
<td>17(46)</td>
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<td>Haenek 1999</td>
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<td>Ph</td>
<td>10</td>
<td>nr</td>
<td>60(73)</td>
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<td>Holmström 1999</td>
<td>RE</td>
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<td>Ph</td>
<td>5-14</td>
<td>nr</td>
<td>195(76)</td>
<td>nr</td>
<td>11(4)</td>
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</table>

nr: not reported, PF: prospective follow-up, RE: retrospective evaluation, RT: randomised trial.
† Including only patients effectively evaluated during follow-up; in parentheses is the number of limbs used as denominator to calculate the prevalence of PTS. ‡ Objective diagnostic methods for DVT: Ph: ascending phlebography, D: Duplex ultrasonography, Cfd: color-flow duplex. § Mean or range follow-up (years). ¶ Actual number of patients using stockings on a regular basis, expressed as n(%). ** Cumulative incidence after 8 years of follow-up. †† Study limited to patients with calf vein thrombosis.
This scale had been developed in a separate series of patients with overt PTS and patients without any sign and symptom of the syndrome after an episode of DVT, and had shown a high reproducibility and correspondence with patient's quality of life. Of the 355 patients, 84 (24%) developed the PTS, that turned out to be severe in about 30%. The cumulative incidence of PTS was 17.2% after 1 year, and 22.8% after 2 years of follow-up. Thereafter, the cumulative incidence of PTS increased gradually until 28.0% at 5 years, but did not substantially increase afterwards. Considering only the severe post-thrombotic manifestations, the cumulative incidence rose constantly from 2.6% after 1 year to 9.3% after 5 years, and did not substantially increase thereafter (Figure). Similar findings were observed after 173 new patients were added to the original cohort of the study. As in the Dutch trial, most of the patients who developed post-thrombotic manifestations became symptomatic within 2 years from the acute episode of DVT. These findings challenge the general view that the PTS requires long time to develop, and suggest that severe post-thrombotic manifestations are relatively uncommon in patients adequately treated with anticoagulants and wearing elastic compression stockings. These conclusions are supported by the results of at least two other recent studies.

Table 2 - Standardized scale for the assessment of post thrombotic syndrome.

<table>
<thead>
<tr>
<th>Subjective symptoms*</th>
<th>Objective signs*</th>
</tr>
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<tbody>
<tr>
<td>Heaviness</td>
<td>Pretibial edema</td>
</tr>
<tr>
<td>Pain</td>
<td>Induration of the skin</td>
</tr>
<tr>
<td>Cramps</td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Pruritus</td>
<td>New venous ectasia</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Redness</td>
</tr>
<tr>
<td></td>
<td>Pain during calf compression</td>
</tr>
<tr>
<td></td>
<td>Ulceration of the skin</td>
</tr>
</tbody>
</table>

Definition of post-thrombotic syndrome:
Severe: ulcer in one occasion or score ≥ 15 measured in two consecutive visits
Mild to moderate: score between 5 and 14 in two consecutive visits
Absent: score ≤ 4

*Each sign or symptom was graded with a score between 0 and 3. The presence or absence of leg ulcer was noted.
Figure - The cumulative incidence of overall and severe post-thrombotic syndrome 8 years after an episode of venographically proven deep venous thrombosis in 355 patients.

Pathophysiology and determinants of PTS development

The PTS develops as a result of the combination of venous hypertension, due to persistent outflow obstruction and/or valvular incompetence, with abnormal microvasculature or lymphatic function. Long-standing venous hypertension in the deep-vein system ultimately leads to the onset of valve incompetence at the level of a constant series of perforating veins located in the medial ankle area. This allows the direct transmission of the high deep-venous pressures (especially during walking) to the venous end of subcutaneous capillaries, resulting in increased endothelial permeability. Escaping of large molecules into the interstitial tissue may, in turn, explain the typical pattern of oedema, hyperpigmentation and even ulcer formation. A recent hypothesis postulates that an increased venous pressure standing or walking causes a reduction in capillary flow rate, resulting in trapping of white blood cells in the leg and the subsequent release of free radical and proteolytic enzymes ultimately responsible for the venous ulceration.

The presence of reflux in the proximal veins appears to be crucial for the development of PTS. This is supported by the finding of a strong relationship between the thrombotic involvement of the popliteal vein and the development of PTS, as venous reflux develops more frequently in venous segments
affected by DVT. The influence of reflux in areas other than the popliteal vein is less clear, although severe PTS appears to correlate with the presence of venous insufficiency in the superficial, or both the deep and the superficial venous systems. According to the results of a few studies, persistent venous obstruction, alone or in combination with venous reflux plays an important role in the PTS development.

Although some authors suggested that the initial extent of thrombosis and its degree of occlusiveness were related to the risk of developing PTS, this was not confirmed by many other investigators. Thus, patients with a minor proximal DVT (i.e., involving the popliteal vein only) or with isolated calf-vein thrombosis, are as likely to develop late sequelae as patients with extensive DVT involving the whole leg and the pelvis.

A strong relationship between ipsilateral DVT recurrence and the development of PTS has been reported by several authors. Accordingly, an appropriate prophylaxis of recurrent DVT through the identification of the optimal duration of oral anticoagulant therapy following the initial thrombotic episode might play an essential role for prevention of late post-thrombotic sequelae.

Clinical and instrumental diagnosis

Clinical diagnosis and scoring systems

The syndrome is characterised by aching pain on standing, dependent oedema, and the frequent development of brawny, tender induration of the subcutaneous tissues of the medial lower limb, a condition that has been termed "lipodermatosclerosis". Pruritus and eczematous skin changes are frequently present, and a proportion of patients develops secondary superficial varicose veins as the syndrome evolves. Ulceration, often precipitated by minor trauma, arises in a considerable number of patients and is characteristically chronic and indolent with a high recurrence rate, once healing has been achieved. Uncommonly, patients with persistent obstruction may experience venous claudication, a bursting pain in the leg during exercise, which, in some respects, mimics arterial claudication. The clinical picture of the PTS is aspecific, as other conditions than DVT may result in a comparable set of signs and symptoms to that affecting the lower extremities of patients with a previous DVT, including superficial venous insufficiency, old age, increased body mass index, and traumas.

The diagnosis of PTS is essentially based on the development of the above-mentioned clinical manifestations in patients with a history of DVT, irrespective of
the presence of venous abnormalities as shown by invasive or non-invasive diagnostic procedures. In the absence of signs and symptoms, the demonstration of venous abnormalities (such as venous reflux, persistent venous obstruction, or both) does not allow the definition of a patient with a history of DVT as having a PTS.

Although the picture of PTS is classic, there is large variation between published studies as to its clinical classification. To our knowledge, two standardised approaches are available from the literature, and deserve further consideration. The first, based on clinical findings alone, has been used for the scoring of PTS in the two recent prospective trials (Table 2).17,18,24,25

The second, also known as CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification, spreads form the cooperative work of a panel of experts in the fields of vascular disease, and combines clinical and objective findings into a sophisticated scoring system.45

Instrumental diagnosis

If a patient with a history of a previous (documented or highly suspected) DVT develops symptoms and signs compatible with PTS, there is no need for further investigation. As the clinical picture is quite aspecific,26,42-44 the need for objective confirmation arises in patients with leg complaints and without likely or proven history of DVT. Ascending phlebography is potentially useful to detect a previous DVT. Suggestive findings include narrowing or occlusion of the deep veins, contrast dye opacification of fewer veins (than normal) or perfusion of superficial or deep collateral veins. Recanalised veins show irregular margins, bizarre-appearing or multi-channeled lumen with webs, and usually have reduced calliper due to fibrotic thickening of their walls. Such veins may subsequently become dilated, probably because of loss of their elastic tissue.46

Despite the predictive value of these venographic patterns in patients with possible PTS, the invasiveness and cost of phlebography makes such an approach not applicable to most patients with a history of clinically suspected DVT.

We have recently shown that the combination of standardised clinical evaluation with compression ultrasonography and continuous-wave Doppler analysis can reliably diagnose or exclude a prior proximal-vein thrombosis in almost 90% of patients with a suggestive history.47 Compression ultrasonography should be performed first, checking the popliteal and the common femoral vein for compressibility as previously described.48 If either or both veins are incompressible, then a definite diagnosis of previous (proximal) DVT is made.47
Unfortunately, the usefulness of ultrasound tapers off over time, as vein incompressibility is detectable in just 30% of the patients after more than 5 years.\cite{47,49}

Patients with normal ultrasound test results are interviewed and examined according to a standardised form, whose high reproducibility has been recently demonstrated (Table 2),\cite{24} and subsequently undergo continuous-wave Doppler analysis to test valve function, both in the common femoral and in the popliteal vein. The finding of both a popliteal reflux and/or of a clinical score greater than 8 is highly specific for the adjudication of a prior DVT in patients with normal ultrasound test result.\cite{57} On the other hand, if ultrasound testing is normal, deep venous reflux is absent, and the clinical score is less than 8, then previous proximal venous DVT is practically excluded.\cite{47}

The widespread availability of Duplex scanners renders our approach even more rapid and precise, as they allow for venous flow sampling during direct visualisation of the vessels.\cite{22,36,40,50} In addition, color-coded Duplex is promising in this context, as it enables the demonstration of typical flow irregularities inside the recanalised veins.\cite{31,31,33}

Besides the demonstration of previous episodes of DVT, either invasive or non-invasive methods can be employed to document and quantify the presence of obstruction, reflux, or both, that are considered the major determinants of PTS.\cite{12,16,22,35,37,39,41,54} Duplex ultrasound, performed with the patient standing, is the preferred non-invasive method for quantifying reflux.\cite{45}

Finally, preliminary results suggest a potential usefulness of some of these techniques for the early identification of patients at higher risk of developing (severe) PTS.\cite{11,31,36,38} Prospective studies on wide series of patients would be required to confirm these interesting findings.

**Treatment of PTS**

Once established, PTS, especially when complicated by leg ulcer, is a significant cause of disability with a considerable economical burden for both the patients and the health care services.\cite{1,26,27,30,32,55} The management of this condition is demanding and often frustrating. Several treatment strategies, both conservative and surgical, were tested, especially aimed at ulcer healing.

**Conservative treatment**

Compression therapy, either obtained with short stretch bandages, adhesive bandages, multiple layer bandages (with orthopedic wool plus compressive layers), stockings, or zinc bandages, and frequent leg elevation are the corner-
stones of the conservative management of venous ulcer. Irrespective of the choice, effective compression therapy is obtained with implements exerting a 35 to 40 mm Hg pressure at the ankle. Greater benefits (higher, faster healing, and low recurrence rates) are to be expected if compliance with compression therapy is monitored through ambulatory care programs, and patients are encouraged to take regular exercise and to elevate the extremities while resting.

In addition to compressive therapy, a number of active compounds have been evaluated in a series of small randomised trials for the healing of venous ulcers. Among these pentoxifylline, aspirin, intravenous prostaglandin E1, sulphydryl containing agents (DL-cysteine or DL-methionine), and radical scavengers (allopurinol or dimethyl sulfoxide), significantly improved the ulcer-healing rate.

As regard to other manifestations of PTS, three small randomised trials demonstrated some beneficial effect of intermittent compression therapy on intractable pain and severe swelling, that of an anabolic steroid (stanozolol) plus elastic stockings on lipodermatosclerosis, and that of 0-(b-hydroxyethyl)-rutosides on edema and several milder PTS symptoms, respectively.

**Surgical treatment**

Surgical is often advocated when clinical manifestations (ulcer) cannot be managed by conservative treatment: various strategies are available, among whom subfascial perforator legation and valvuloplasty appear to be the most promising. A recent trial on subfascial endoscopic perforator surgery plus correction of superficial venous reflux indicates that, although effective in improving symptoms and ulcer healing in patients with primary venous insufficiency, this procedure is not as effective in patients with PTS. Similarly, deep (femoral-popliteal) valve reconstruction surgery performed after unsuccessful endoscopic perforator surgery, and correction of superficial venous reflux, yields significantly better results in patients with primary venous insufficiency, than in patients with PTS.

**Prevention of PTS**

*Initial treatment of DVT*

Thrombolysis and thrombectomy have been traditionally advocated as alternative strategies to heparin for the initial treatment of DVT, based on the assump-
tion that a preserved venous function warrants a more favourable long-term outcome.\textsuperscript{30,71,72} These strategies result in a higher frequency of early vein patency, as compared to heparin.\textsuperscript{71-74} However, they are associated with a higher risk of complications. In addition, although data on the long-term follow-up of patients treated with thrombectomy or thrombolytic drugs are scarce, the rate of clinically relevant post-thrombotic sequelae does not appear to differ from that of patients receiving anticoagulants alone.\textsuperscript{73-77} Thus, the routine use of aggressive therapies for the prevention of long-term sequelae of DVT does not seem to be currently justified.

In recent years, low-molecular weight heparins have become the first therapeutic option for the initial treatment of proximal DVT.\textsuperscript{78} However, no significant differences in terms of PTS scores were observed between patients randomly allocated to low-molecular-weight or unfractionated heparin after 14 years of follow-up.\textsuperscript{23}

**Elastic compression stockings**

Aside from the initially chosen treatment strategy, elastic compression therapy is usually prescribed for at least 6 months after the DVT episode.\textsuperscript{8,17,22,71} This procedure is supported by the results of a randomised long-term follow-up study,\textsuperscript{38} and by those of other cohort studies.\textsuperscript{2,13,14,16,17,41}

**Prognosis**

It is common belief that patients with established PTS have a poor prognosis, and that the majority will undergo a long lasting invalidation.\textsuperscript{1,26,30} In recent years, a few reports have suggested that that prognosis of PTS might not be as poor as previously reported.\textsuperscript{57-59} Indeed, when provided elastic compression stockings and regularly supervised, more than 50\% of patients either remain stable or improve during long-term follow-up, irrespective of the initial degree of PTS.\textsuperscript{57-59} Clinical presentation helps predict the prognosis, being the outcome of patients who refer with initially severe manifestations more favourable than that of patients whose symptoms progressively deteriorate over time.\textsuperscript{59}

**Conclusions**

Approximately 30\% of patients with a first episode of DVT will develop postthrombotic manifestations. This incidence is considerably lower than rates suggested from early clinical trials. Most of the cases of PTS develop within 2 years
from the thrombotic event, and apparently are not related to the initial extent of venous thrombosis. The development of ipsilateral recurrence of DVT carries a high for severe post-thrombotic manifestations, otherwise rare in patients with a first episode of DVT adequately treated with anticoagulant drugs and wearing compression elastic stockings. Although the prognosis of PTS is less unfavourable than believed in the past, severe PTS remains a significant cause of disability with a considerable economic burden for both the patients and the health care services. Prevention of recurrent thrombosis and use of proper elastic stockings help minimise the risk of such long-term complications of venous thrombosis.

References


