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Prospective Studies on Diagnosis, Prevention, and Management of Deep Vein Thrombosis (DVT), DVT Recurrence and the Post-Thrombotic Syndrome (PTS): From Concept to Study Design in the Primary Care Setting

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Abstract

The requirement for a safe diagnostic strategy of deep vein thrombosis (DVT) should be based on an overall objective post incidence of venous thromboembolism (VTE) of less than 1% during 3 months follow-up. Compression ultrasonography (CUS) of the leg veins has a negative predictive value (NPV) of 97% to 98% indicating the need of repeated CUS testing within one week. A sensitive ELISA VIDAS safely excludes DVT and VTE with a NPV between 99 and 100% when the clinical score is low to zero. The combination of low clinical score and a less sensitive D-dimer test (Simply Red or Simplify) is not sensitive enough to exclude DVT and VTE in routine daily practice. From prospective clinical research studies it may be concluded that complete recanalization within 3 months and no reflux is associated with a low or no risk of PTS obviating the need of MECS 6 months after DVT. Partial and complete recanalization after 3 to more than 12 months is usually complicated by reflux due to valve destruction and symptomatic PTS. Reflux seems to be a main determinant for not only for PTS and but also for DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT=partial recanalization) and the risk of VTE recurrence in prospective studies. Absence of RVT at 3 months post-DVT and no reflux is predicted to be associated with no recurrence of DVT (1.2%) during follow-up obviating the need of wearing medical elastic stockings and anticoagulation at 6 months post-DVT. The presence of RVT at 3 months post-DVT with reflux after 6 months post-DVT is associated with both symptomatic PTS and an increased risk of VTE recurrence in about one third in the post-DVT period after regular discontinuation of anticoagulant treatment. To test this hypothesis we designed a prospective DVT and PTS Bridging the Gap Study by addressing at least four unanswered questions in the treatment of DVT and PTS. Which DVT patient has a clear indication for long-term compression stocking therapy to prevent PTS after the initial anticoagulant treatment in the acute phase of DVT? Is 3 months the appropriate point in time to determine candidates at risk to develop DVT recurrence and PTS? Which high risk symptomatic PTS patients need extended anticoagulant treatment? Patients with acute ileofemoral DVT are at very high risk of PTS and candidate for cather-directed thrombolysis followed by anticoagulation.

Keywords: Deep venous thrombosis; Ultrasonography ; Doppler duplex; Post-thrombotic syndrome; Elisa D-dimer; Medical elastic stockings; Anticoagulation

Deep-Vein Thrombosis (DVT)

Epidemiology

DVT has an annual incidence of 0.2% in the urban population [1]. The disease is rare in children under 15 year of age, but its frequency increases with age, with an incidence of 1.8 per 1000 persons-years at age 65 to 69 years and 3.1 per 1000 persons–years at age 85 to 89 years [2,3]. First-time episodes of DVT are in two-thirds of cases elicited by risk factors, including cancer, immobility, or surgery. The prevalence of DVT is comparable in black and white adults and is low in Asian populations. Risk for DVT seems to be slightly higher in men than in women, and the risk of recurrence of venous thromboembolism is about 60% higher in men compared to women [4].

Pathogenesis

In 1856, Virchow postulated that the main causes of thrombus formation consist of damage to the vessel wall, alterations in flow, and hypercoagulability and this model is called 'Virchow's triad' and is still valid today [5]. The maintenance of the fluidity and circulation of the blood and its ability to thrombosis are essential for the maintenance of life and are governed by extremely complex homeostatic mechanisms. The mechanisms of thrombosis, a protective device to prevent loss of blood and to seal off a damaged blood vessel, and of fibrinolysis, which counteracts or stabilizes the effects of thrombosis, depend upon systems of consecutive enzyme activity with activators and inhibitors finely balanced at every stage. Alterations in blood coagulability, platelet population and agglutinating power, with changes in blood flow and endothelial damage, are the precursors of intravenous thrombosis. Of these, the loss of normal function of the vascular endothelium is probably of primary importance [6]. Anticardiolipin antibody is also now recognized as an important cause of thrombosis [7-9]. A number of other hereditary and acquired conditions that predispose to thrombosis (thrombophilia) have been recognized. These include protein C and S deficiency, antithrombin III deficiency, activated protein C resistance (which is usually associated with a factor V genetic abnormality) factor II G20210A mutation and lupus anticoagulans [2,10-12]. Screening for these congenital thrombophilic factors, and for anticardiolipin antibody, should be performed in patients having sporadic or recurrent

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thrombosis [11,12]. Oral contraceptive use is a common risk factor for venous thromboembolism in women of reproductive age [13]. Surgical operations and pregnancy remain important triggers, and prolonged immobility as in long-haul flights, or hormonal influences, such as the contraceptive pill, are also well-documented risk factors [14].

Clinical features

The onset of a thrombosis is often 'silent' and may remain so. It commonly occurs at or about day 7 to 10 after a surgical operation, parturition or the onset of an acute infection, concomitant with a rise in fibrinogen and platelet count. Between one-third and two-thirds of patients complain of some swelling and pain in the leg, usually in the calf [4]. An iliac vein thrombosis should be suspected if the whole leg is swollen and dusky. Direct pressure on the calf muscles or over the course of the deep veins usually elicits direct tenderness. There may be a cyanotic hue to the leg and superficial venous dilatation. The temperature of the leg may be raised, and oedema of one ankle is an important physical sign. However, chest pain or cardiac arrest from pulmonary embolism is often the first indications of a DVT. Pulmonary hypertension may follow repeated small emboli, and is associated with the development of progressive dyspnoea.

Differential diagnosis

Pain and tenderness in the calf and popliteal fossa may occur resulting from other conditions such as a ruptured Baker's cyst, a torn plantaris tendon, a hematoma, or muscle tears or pulls. Cutaneous infection (e.g. erysipelas, cellulitis), lymphoedema, venous reflux, specially hypodermatitis, peripheral arterial disease, neurological and rheumatological causes should also be differentiated from DVT.

Diagnosis

Accurate diagnosis is mandatory in patients with suspected DVT, as an untreated thrombus may lead to pulmonary embolism, and anticoagulation in the absence of thrombosis is irresponsible [15-17]. Because only a quarter of patients with suspected DVT actually has the disorder, it is important to safely rule out thrombosis by non-invasive, rapid, and cost-effective methods. As compared with phlebography (the reference gold standard to exclude and diagnose proximal DVT randomized clinical trials), the sensitivity of compression ultrasound (CUS) is 97% for proximal and 73% for distal vein thrombosis. CUS has many advantages over phlebography. It is noninvasive, simple, easy to repeat, relatively inexpensive, and free of complications [18]. It is safe to limit CUS estimation to the subpopliteal, popliteal, and femoral veins for the diagnosis of symptomatic proximal DVT [19,20]. However, there are two main disadvantages of CUS. First, calf vein thrombosis will be overlooked by CUS but may progress to proximal DVT indicating the need to repeat CUS after one week. Second, isolated thrombi in the iliac and superficial femoral veins within the adductor canal are rare but difficult to detect and therefore easily overlooked in symptomatic patients with suspected DVT [16,17].

To date, the sequential use of a sensitive quantitative D-dimer test, clinical score, and CUS appears to be safe and the most cost-effective diagnostic work-up of DVT (Figure 1 and Table 1) [15-17,21]. Estimates of clinical score as low, moderate, and high for the probability of proximal DVT, based on medical history and physical examination, is the first step when DVT is suspected (Table 1). A score of 0 (asymptomatic) means a low probability, a score of 1 or 2 a moderate probability, and a score of 3 or more a high probability for DVT (Table 1).

D-dimer is a degradation product of a cross-linked fibrin clot. It has gained a prominent role for ruling out DVT because of its high sensitivity [22]. However, the specificity of D-dimer is low because its concentrations can be raised in various other conditions, such as inflammation, pregnancy, or cancer [3,16,17,22].

A normal quantitative ELISA VIDAS D-dimer test (cut-off <500 ug/L) was reported to have a 100% sensitivity when compared with phlebography in two studies [23,24]. In the large prospective studies of outpatients with suspected DVT, the sensitivity varied between 98% and 99.9% in 2239 patients, irrespective of clinical score [25-27]. In two large outcome studies, the sensitivity of a normal turbidimetric assay (Tinaquant, cut-off <500 ug/L for the exclusion of DVT varied from 91% to 98% and the specificity from 44% to 51% [26-28]. The qualitative D-Dimer test Simply Red has a sensitivity of 89%, a specificity of 77% and a NPV of 96% for the exclusion of DVT [29]. Similarly, the quantitative ELISA VIDAS test at a cut of level of 1000 ug/ml has a sensitivity of 88% to 89%, a specificity of 56% to 68% and a NPV of 96% in two large studies [16,17,30].

The general application of DVT exclusion by a negative SimpliRed (Simplify) by the combination of a negative CUS and low clinical score is not safe enough mainly because the prevalence of DVT in the low clinical score group may vary widely (3% to 12%) [17,27]. After a first negative CUS the prevalence of DVT is uniformly low, 2% to

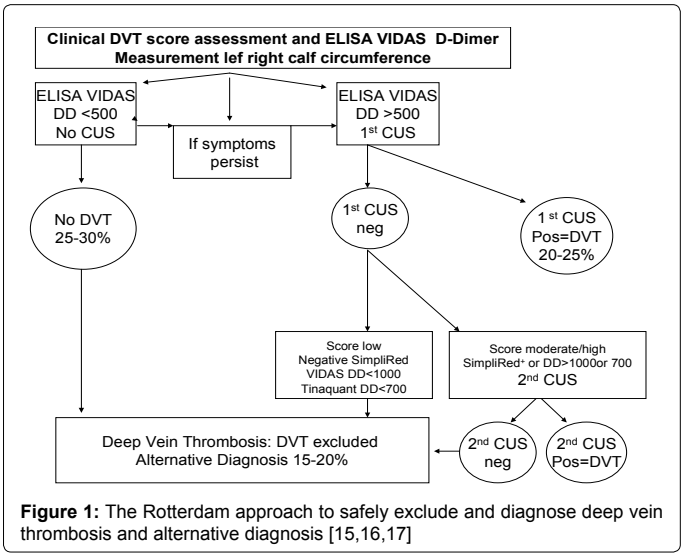


Figure 1: The Rotterdam approach to safely exclude and diagnose deep vein thrombosis and alternative diagnosis [15,16,17]

Clinical feature	Score
Active cancer treatment ongoing or within previous 6 months or palliative	1
Paralysis, paresis, or recent plaster immobilization of the lower leg(s)	1
Recent immobilization for more than 3 days or major surgery within last 4 weeks	1
Localized tenderness/pain along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 2 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema greater in the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Total Rotterdam DVT score	**8**
Score 0 (asymptomatic) = low, score 1 or 2 = moderate, score 3 or more = high	

Tabel 1: Clinical score list for predicting pretest probability for proximal DVT The Rotterdam modification [16,17] of the Wells' clinical score assessment [15].

3% [16,17,31-34]. Consequently, the combination of a first negative CUS, low clinical score, and a D-dimer level of ELISA VIDAS <1000, Tinaquant <800 ug/ml or negative SimpliRed (Simplify) will exclude deep vein thrombosis with a NPV of more than 99% in 4 prospective outcome studies [17,31-33]. A moderate to high probability and/or increased a ELISA D-dimer (VIDAS >1000 or Tinaquant >800 ug/ml) or a positive qualitative D-dimer (SimpliRed or Simplify) should be followed by a second CUS of the legs after one week (12,13) to detect a thrombus in about 3% of patients [16,17,31-34].

Complications

Pulmonary embolism, post thrombotic syndrome (PTS) and recurrent thrombosis are the main complications of DVT. If proximal DVT is left untreated, clinical pulmonary embolism will occur in 26 to 67% of the cases, and is associated with a mortality rate of 11 to 23% [35,36]. The incidence of pulmonary embolism decreases to 5% and the mortality to less than 1% under anticoagulant treatment [35]. About 10 to 30% of patients with DVT develop PTS. DVT has a recurrence rate of about 20% to 30% after 5 years, but the rate varies depending on the presence of risk factors [36-39].

Prevention

In the prospective study of Scurr et al in 1977, medical elastic stockings reduced the incidence of post-operative DVT from 30% to 10% in patients after major abdominal surgery [40]. Below-knee stockings appear to be as effective as thigh-length hosiery. MECS may also be used combined with low-dose unfractionated heparins (LDUH) or low-molecular weight heparins (LMWH), and other pharmacologic or mechanical means of thrombosis prophylaxis [41]. Pneumatic compression therapy has been proved to be effective, but is probably only realistic in post-operative circumstances, and it has shown to be effective in for example elective knee or hip replacement [21,42].

Dermatologists should be aware of risk factors for DVT, particularly in elderly bedridden inpatients with widespread skin disease, infection, or other comorbidities. The incidence of DVT among general medical patients with reduced mobility ranges from 10 to 26% [42]. Prolonged sitting is as harmful as lying. Active exercise and early mobilization is desirable when possible. All hospitalized general medical patients should be assessed for venous thromboembolism risk factors [41]. Those patients classified to be at moderate at high risk should be given thrombosis prophylaxis with LDUH (preferably 5000 U three times a day) or LMWH (4000 U or more once daily).

Surgical patients may be classified as having a low, moderate, or high thromboembolic risk. Low risk patients are patients under 60 years of age without any other risk factors for venous thromboembolism undergoing minor surgery (e.g. laparoscopic surgery, transurethral surgery, or out-patient surgery). These patients should be mobilized early and no additional thromboprophylactic regimen is required. The group of moderate risk patients consists of patients older than 60 years undergoing minor surgery, and patients younger than 60 years who undergo major surgery, but have no additional risks. These patients should be anticoagulated with LDUH (every 12 hours) or LMWH (≤3400 U daily). Patients with high bleeding risk may be treated by MECS or intermittent pneumatic compression alone. High risk patients for venous thromboembolism are patients undergoing major surgery and being over 60 years of age, or having additional risk factors. These patients should be treated with LDUH (every 8 hours) or LMWH (>3400 U daily). MECS may be used as additional treatment [41,42].

Patients undergoing major orthopedic surgery face an overall DVT rate ranging from 40 to 60% and a proximal DVT rate between 10 to 30% without thrombosis prophylaxis. The general consensus is that these patients receive adequate thrombosis prophylaxis with LMWH, because these have proven to be more effective than LDUH. Moreover, patients receiving prolonged treatment duration (4 to 5 weeks) in hip surgery showed a significant reduction of DVT rate [41,42].

Treatment

The diagnosis should be confirmed as soon as possible by compression ultrasound if a DVT is suspected. Initial treatment with a LMWH is given subcutaneously once a day (150 to 200 IU/kg). LMWH is superior to LDUH for initial treatment of DVT [3,41,42]. LMWH is also effective in an outpatient setting, and compared to LDUH it has a more predictable dose-response relationship, a longer half-life, and assigns a lower risk for osteoporosis and immune-mediated thrombocytopenia [3,41]. As soon as the diagnosis of DVT is confirmed, vitamine K antagonists (e.g. warfarin) should be added to the heparin. Monitoring of anticoagulation is done by the prothrombin time, expressed in terms of the international normalized ratio (INR). A ratio between 2.0 and 3.0 should be achieved for the most adequate anticoagulation, and the lowest risk of bleeding. Heparin can be discontinued after 5 to 7 days, as long as the INR is stable and 2.0 or greater [3,41]. Idiopathic venous thromboembolism is generally treated for 6 months, but anticoagulation may be for life for those with continuing risk [43].

LMWH and oral anticoagulants should be combined with ambulatory compression. Once oedema has been reduced completely, class II MECS (23 to 32 mm Hg at B measurement) is prescribed to be worn for a period of 2 years. If, during the use of MECS, oedema is still present, class III MECS (34 to 46 mm Hg at B measurement) are prescribed [44]. MECS significantly reduce the development of post-thrombotic syndrome.

Vena cava filters are effective in preventing the short-term incidence of pulmonary embolism in patients with proximal DVT, but they do not affect mortality. Vena cava filters are thrombogenic and double the recurrence risk of DVT [3].

Post-Thrombotic Syndrome (PTS)

Definition

The post thrombotic syndrome (PTS) is a chronic condition that affects the deep venous system, and may also extend to the supeficial venous system of the legs in patients with a documented history of deep vein thrombosis (DVT) [1,44,45].

Incidence

The incidence of symptomatic PTS grade 3 to 4 is about 10% 1 year after an episode of DVT, and increases to about 50% over a period of 5 to 8 years. The only clear identified risk factor for PTS is recurrent or ipsilateral DVT, which increases the risk of PTS as much as 6-fold [1,45]. About one third of DVT patients develop PTS within 5 years [2,3,37-39].

Pathophysiology of PTS

Venous hypertension plays a key role in the pathophysiology of PTS [1,45,46]. This venous hypertension in turn is caused by a combination of several factors, among which are valvular incompetence leading to reflux, outflow obstruction, and dysfunction of the calf muscle pump. Both the deep and the superficial venous system contribute to the development of PTS. After initial thrombosis, lysis of the thrombus

may start. Propagation of the thrombus also occurs; the two processes occur simultaneously, whereby recanalization and the formation of a new thrombus are competing processes. Recanalization may be completed after 3 to 6 months without reflux or may be delayed up to more than 1 year with a high incidence of reflux development and DVT recurrence (Figure 2) [47,48]. During these processes, which may continue for as long as 24 months, venous valves are destroyed and residual obstruction of the vein may persist in only about 10% [35].

As shown in Figure 2, loss of valve competence leading to ambulatory venous hypertension (AVP) and diversion of venous flow through incompetent perforans veins appear to play an important role in the development of late complications of PTS [47,48]. Anatomic studies have described the most distribution of venous valves to be a single valve in the common femoral vein (CFV) above the sapheno femoral junction, a relatively constant deep valve just before its termination in the CFV, three to four valves in the superficial femoral vein with relatively constant locations at the mid-thigh and adductor canal, one or two valves in the popliteal vein (PPV) and one to two valves with the terminal 2 to 2 cm of the grater saphenous vein (GSV). Among the calf veins, the popliteal vein (PPV) appears to be of primary importance in the development of the post-thrombotic syndrome, by virtue of both its importance in the calf muscle pump and its communications with the posterior arch vein. Meissner et al studied the relationship between complete recanalization (lysis time) and the development of reflux in patients with a first episode of DVT at 3months interval during the first year (Figure 2) [47]. Duplex criteria for complete occlusion were defined as the absence of detectable flow, either spontaneous or with augmentation, in an incompressible venous segment. Partial occlusion was defined as normal or diminished flow, either spontaneous or with augmentation, in an incompletely compressable venous segment. Complete lysis (recanalization) was presumed to have occurred when spontaneous phasic flow returned and the vein was completely compressable [47]. The median time from DVT to complete recanalization (lysis time) was about 3 months (100 days) for patients without reflux in all segments (Figure 2) [47]. In contrast, the median time from DVT to complete recanalization (lysis time) of all segments was about 9 to 12 months (more than 6 months) for DVT patients who developed reflux in the popliteal and femoral veins as, the main determinant of PTS (Figure 2) [47]. In the study of 123 legs with DVT (107 patients) by Markel et al about two third of the involved legs had developed valve incompetence [48]. The distribution of reflux at the end of the first year follow-up in this study was the following: popliteal vein, 58%, superficial femoral vein, 37%, greater saphenous vein, 25% and posterial polpliteal vein, 18%. Reflux appeared to be more frequent in the segments previously affected by DVT [48].

From these two prospective clinical research studies [47,48] it may be concluded that complete recanalization within 3 months and no reflux is associated with a low or no risk of DVT recurrence and PTS obviating the need of MECS 6 months after DVT (Table 3). On the other hand, partial and complete recanalization after 6 to more than 12 months is usually complicated by reflux due to valve destruction [47,48]. Consequently, reflux seems to be a main determinant for not only for PTS and but also for DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT= partial recanalization) and the risk of VTE recurrence in two prospective studies [49,50]. In a recent study (49), RVT at 3 months post-DVT was absent in 30%, which was associated with no recurrence of DVT (1.2% during two years follow-up (Table 2). In contrast, the presence of RVT at 3 months post-DVT was associated with a DVT recurrence rate of 27% during two years follow-up after discontinuation of anticoagulant treatment (Figure 3). In a previous prospective study of 313 consecutive DVT patients, Prandoni et al. have shown that RVT at any time post-DVT is a risk factor for recurrent VTE [50]. In this study, CUS of the common femoral and popliteal veins was performed at 3, 6, 12 24 and 36 months post DVT. The cumulative incidence of normal CUS (no RVT) was 39%, 58%, 69% and 74% at 6, 12, 24 and 36 months post DVT respectively. Of 58 VTE recurrent episodes, 41 occurred at time of RVT. The hazard ratio for recurrent VTE was 2.4 with persistent RVT versus those with earlier complete vein renalization [50].

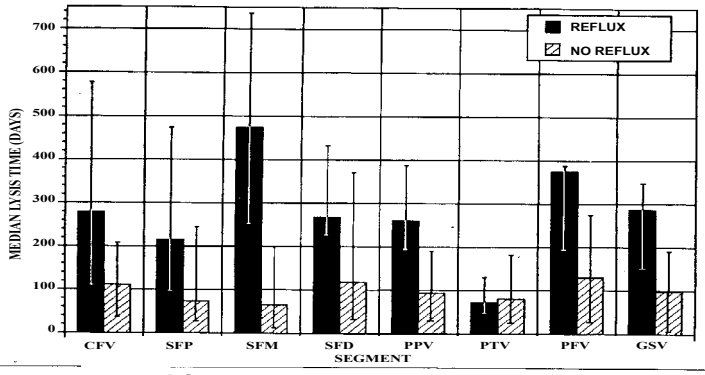
Palareti et al. and other studies showed that normal versus increased D-dimer levels one month after discontinuation of regular anticoagulation is associated with an incidence of about 5% pt-years and 10 to 15% pt/years respectively [51-53]. This difference was independent from other factors like thrombophilia or residual venous occlusion [51,52]. In the PROLONG study, extended anticoagulation reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer [54]. These data has to be interpreted in view of two other key observations: first the incidence of DVT recurrence after complete recanalization within 3 months and no reflux is very low [47,49]. Second the incidence of PTS in the control arm of two randomized clinical trials was about 50% within 6 months and did not significantly increase thereafter, whereas MECS decreased the incidence of PTS from around 50% to 25% after two years follow-up [55,56]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer do occur in those with incomplete or complete RVT after 3 months with reflux (Table 2). The hypothesis, summarized in Table 3 that the Rotterdam scoring system for PTS will have therapeutic implications, has to be tested by the use of objective measurements of RVT and reflux related to clinical score for PTS in prospective management and outcome studies.

Scoring Systems for PTS and Chronic Venous Insufficiency (CVI)

General considerations

Accepted diagnostic criteria exist for the diagnosis of DVT. No uniform definition for PTS exists. The ability of various scoring systems to discriminate between DVT and control legs as well as the observed prevalence of PTS and CVI differed substantially [45]. Many theories and at least three classifications (the Widmer, CEAP, Venous Clinical Severity, VCS, scores) have been put forward to explain the late symptoms of chronic venous insufficiency (CVI) of various etiologies. A multi-causal model, also known as the Maastricht model, explains the signs and symptoms of CVI [45,46,57-60]. Increased venous pressure leads to leakage of fluid and proteins and thus to an acute inflammatory process known as hypodermitis. All of the clinical signs and symptoms of CVI are based on the dysfunction of the venous circulation that, in turn, is caused by the changes in the macro circulation. Formation of sclerotic plaques in the skin counteracts the normal movements of the ankle joint, resulting in a partial secondary failure f the calf muscle pump and chronic compartment syndrome.

The fundamental pathophysiologic disturbance with severe leg symptoms or sign after distal and proximal DVT is sustained venous hypertension, which result from valvular incompetence, venous outflow obstruction, calf muscle dysfunction, or a combination of these. Sustained venous pressure can be measured with invasive venous



	Reflux			No reflux			
Segment	*n*	*Median lysis time (days)*	*Interquartile range*	*n*	*Median lysis time (days)*	*Interquartile range*	*p Value*
CFV	10	278	104-577	14	111	37-208	0.14
SEP	15	214	95-474	18	73	30-245	0.086
SFM	10	471	245-736	16	65	15-199	0.002
SFO	7	268	230-433	13	118	34-371	0.15
PPV	10	260	187-388	20	93	29-190	0.006
PTV	8	72	49.130	38	80	28-182	0.85
PFV	5	375	289-388	10	130	30-275	0.04
GSV	6	287	145.348	7	98	4.191	0.11

Figure 2: The relationship between the time of complete recanalization after DVT (lysis time) appears to be 3 months for those DVT patients who did not develop reflux, but appeared to be about 6 to 12 months for those DVT patients who developed reflux as a main determinant for the development of PTS (CFV common femoral vein, SFV superficial femoral vein, SFM middle superficial femoral vein, SFD distal superficial vein, PPT popliteal vein, PTV posterior tibial vein, GSV greater saphena vein) [47]

Complete recanalization at 3 months and no reflux	0
Incomplete recanalization at 3 to 12 months	1
Complete recanalization after 6 months and reflux	1
Incomplete recanalization after 6 months and reflux	2
Obstruction after 1 year without or with reflux	2
Normal D-dimer after discontinuation of anticoagulant therapy	0
Increased D-dimer after discontinuation of anticoagulant thereapy	3
Clinical score Brandjes Prandoni score for PTS:	
Absent	0
Mild	1
Moderate	2
Total Rotterdam score	**12**
Score versus:	**Therapeutic implication**
Score 0 at 6 months:	No MECS and no anticoagulant treatment (ACT)
Score 1 to 4 at 6 months:	MECS vs no MECS and continuation of ACT for 2 years
Score 1 to>4 and normal D-dimer at 2 years:	MECS randomization ACT versus no ACT
Score >4 and abnormal D-dimer:	MECS and continuation of ACT according to the PROLONG Plus Study
Designed by Michiels & Neumann 2008	

Table 2: The Rotterdam objective scoring system for grading the severity of PTS during the first two years post-DVT based on prospective studies [46-56]: therapeutic implications

pressure measurement (ambulant venous pressure: AVP). AVP can be regarded as the gold standard, since it directly measures the pressure in the venous system of the lower extremity. This technique requires special equipment, is invasive, time consuming and cumbersome and therefore only suitable for basic research and scientific studies. On the other hand non-invasive equivalents are insufficiently validated.

The identification of no, early and late PTS in patients after a first or recurrent DVT is not reflected by the CEAP classification and remains a challenge for clinicians and phlebologists. Several means of measuring and classifying the early clinical signs and symptoms of PTS and its long-term sequelae of CVI exist. Most scoring systems for PTS are based on the presence or absence clinical signs and symptoms during the first year post-DVT and typical signs of CVI one or few years later. At least five definitions for PTS and/or late CVI exist for the early or long-term complications after an episode of documented DVT. For the prevention and management of PTS, it is crucial that the natural history and treatment outcome of the disease should be documented by additional objective tools including residual vein thrombosis (RVT) on CUS, and reflux and/or obstruction on colour ultrasonography (Table 2).

Diagnostic work-up

At the baseline visit the clinicians should carefully examine the patient's leg to classify the clinical category and to assess the severity of early PTS or late CVI using the different scoring systems. The five scoring systems including the clinical classifications by Brandjes and by Prandoni for early signs and symptoms of PTS during the first year post-DVT, and the CEAP, Widmer and VCS classifications to assess various degrees CVI as late onset sequelae of PTS are presented in Tables 3-7.

Classification of PTS

Two classifications for early PTS has been used by clinicians. The first clinical scoring system of Brandjes was developed in 1991 for early PTS during the first two years after DVT to assess the effect of wearing stockings. It had an equivalent system of subjective signs and objective symptoms, and both are graded as absent or present (Table 3) [55]. The Brandjes scoring system uses separate scales for mild-to-moderate and severe PTS. Mild-to-moderate PTS was defined as score 3 or more including one objective criterion. Severe PTS is assessed separately and

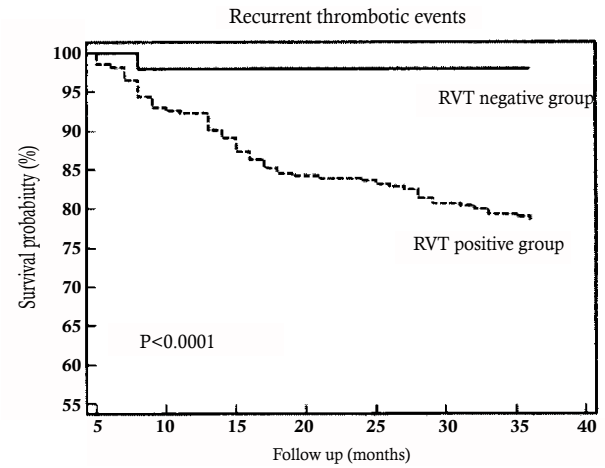


Figure 3: Complete re-canalisation of DVT on CUS at 3 months post-DVT is followed by a very low DVT recurrence rate (1.2%) but partial recanalisation of DVT (Residual Vein thrombosis: RVT at 3 months post-DVT was followed by a high DVT recurrence rate of 27% during 2 years follow-up after anticoagulation discontinuation [49]

Subjective criteria		**Objective criteria**	
Symptoms	**Score**	**Signs**	**Score**
Spontaneous pain in calf	1	Calf circumference ↑ by 1cm	1
Spontaneous pain in thigh	1	Ankle circumference ↑ by 1cm	1
Calf pain on standing/walking	1	Pigmentation	1
Thigh pain on standing/walking	1	Venectasia	1
Edema of foot/calf	1	Newly formed varicosis	1
Heaviness of foot/leg	1	Phlebitis	1
For severe PTS score ≥4 of symptoms and signs			
Symptoms	**Score**	**Signs**	**Score**
Spontaneous pain and		Calf circumference ↑ by 1cm	1
Pain on standing/walking	1	Pigmentation, discolouration	
Edema calf	1	and venectasia	1
Impaiment of daily activities	1	Healed or active ulcer	4

Table 3: Scoring system according to Brandjes for mild-to moderate and severe PTS [55] For mild-to-moderate PTS: score >3 of subjective and objective criteria

consists of a score of 4 or more (Table 3).

As the extension of the Brandjes scoring system, Prandoni developed a simplified clinical scoring system for PTS in a series of patients with overt PTS and patients without any sign and symptoms of PTS and in patients without any sign and symptoms of the syndrome after an episode of DVT (Table 4), and validated his scoring system in prospective studies [37-39,56].

Classification of CVI

Three classifications have been used by dermatologists and phlebologist to describe the severity of CVI, of which the classifications of the CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) (Table 5) [61,62] and Widmer et al. (Table 6) [63] are the best known. The venous clinical severity (VCS) score was developed to provide a slightly more detailed description of the factors contributing to CVI (Table 7) [64].

Clinical features of PTS

During the first year post-DVT, the clinical signs in the early stages of PTS will not always correlate with the severity of the disturbed venous hemodynamics [1]. Patients experience pain, heaviness, swelling, cramps, itching or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing or walking and improve with resting, leg elevation and lying down [55,56,59,60]. Next to varicose veins, a specific sign of early forms of venous incompetence is the so-called corona phlebectatica para plantaris (ankle flare). There are telangiectases surrounding the malleoli of the ankle. Other signs are oedema, hyperpigmentation, and eczema. Signs of more advanced disease are dermato- and liposclerosis, a localized induration of the skin and sometimes of the underlying tissues, with fibrosis and inflammation. Through microthrombi, an area of whitened skin with reddish spots may occur, called "atrophie blanche" or white atrophy. In this sign skin atrophy is accompanied by capillary dilatation and elongation. Finally, the most severe sign is the venous leg ulcer, a

Subjective symptoms	Objective signs
Heaviness	Pretibial oedema
Pain	Induration of the skin
Cramps	Hyperpigmentation
Pruritus	New venous ectasia
Paraesthesia	Redness Pain during calf compression Ulceration of the skin (= severe)
Each sign or symptom is graded with a score as 0, 1, 2, or 3.(0 = absent, 1 = mild, 2 = moderate or interference with daily life and work, 3 = severe or invalidating. The presence or absence of leg ulcer has to be noted.	
Definition of post-thrombotic syndrome according to Prandoni	
Absent:	score <4
Mild-to-moderate:	score between 5 and 14 at 2 consecutive visits
Severe:	score >15 at 2 consecutive occasions or ulcer at 1 occasion

Table 4: Scoring system according to Prandoni for the assessment of post-thrombotic syndrome in the early period 3 to 12 months post-DVT [39,56]

	Symptom
C0 (C = clinical)	No visible varicose veins
C1	Spider or reticular veins
C2	Varicose veins
C3	Oedema
C4a	Pigmentetion or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Skin changes with healed ulceration
C6	Skin changes with active ulceration
S	Symptomatic, including aches, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
C = Clinical symptom	
E = Etiology	Post-DVT
A = Anatomic distribution	Deep, perforator, or superficial vein, alone or in combination
P = Pathophysiologic dysfunction	Reflux or obstruction, alone or in combination

Table 5: Clinical-Etiology-Anatomic-Pathophysiologic (CEAP) classification for severity of chronic venous insufficiency (CVI) [62]

Classification	Symptom
I	Corona phlebectatic paraplantaris (ankle flare), subclinical mild oedema
II	Hyperpigmentation, lipo- and dermatosclerosis, atrophie blanche (white skin atrophy), oedema, eczema
III	Healed or active ulcer

Table 6: Widmer Classification for assessment of chronic venous insufficiency (CVI) [63]

chronic wound that fails to heal spontaneously or within the time range of normal healing of the skin [45].

Clinical symptoms of PTS occurs in about half of the patients within one year post-DVT, may vary considerably and range from scarcely visible skin changes to changes in pigmentation, pain, discomfort, venous ectasia, oedema, and ulceration [55,56,65]. A Dutch study prospectively evaluated the incidence and severity of PTS in 93 DVT patients under careful clinical surveyance using the CEAP classification [65]. This study confirmed previous studies that only half of DVT patients have no clear evidence of PTS (Figure 4). The cumulative incidence of PTS increased from 49% after one year to 55% and 56% after 2 and 6 years, but class 5 and 6 (healed) ulcers did not occur while on treatment with MECS (Figure 4). These symptoms are not distinguisable from those in CVI not caused by DVT [6].

Recommended investigations

A thorough clinical investigation including signs of PTS, arterial insufficiency, and insufficiency of the lymphatic system must be undertaken. It is also necessary to test the range of movement in the ankle and knee joints because impaired movement in the lower leg, especially dorsiflexion of the ankle, reduces the effectiveness of the calf muscle pump [45,46]. The clinical scoring of the severity of PTS using the Prandoni scoring system [39] and CEAP scores [62] should be done by clinic and and phlebologists, but the Widmer scale and VCS scores are optional. Duplex ultrasound is mandatory in all patients, because it provides anatomical and functional information on both the deep and superficial venous systems. Non- or partially recanalized veins can be detected using this technique. Because it is a noninvasive technique, duplex ultrasound may be repeated for a follow-up of these factors contributing to PTS, although one must consider that an inter-observer variability is present. The increase in quality of duplex ultrasound has allowed it to become the gold standard for the diagnosis of venous anatomy and hemodynamics, and the need for phlebography is diminishing. However, if the results of duplex ultrasound are not clear or a venous desobstruction procedure is to take under consideration, phlebography will be the investigation of choice [45].

The gold standard for increased venous pressure related to reflux and obstruction is the direct (invasive) measurement of ambulant venous pressure (AVP), in which a transducer is connected to a vein of the dorsal foot [45,46]. This may be combined with a direct pressure measurement of the compartments of the lower leg. High compartment pressure is associated with severe PTS [45]. The severity of venous reflux also may be indirectly measured using plethysmography. This technique may also be used to measure the capillary filtration rate, which measures the amount of leakage out of the capillary bed of the leg as a part of PTS.

Prevention and treatment

Patients diagnosed with DVT should be treated according to a protocol using low molecular weight heparins, oral anticoagulants, and ambulatory compression [66]. Once edema has been reduced completely, class II MECS are prescribed to be worn for a period of 2 years, significantly reducing the development of PTS [45,57,58]. If during the use of the MECS, edema is still present, class III MECS are prescribed.

Regular follow-up of patients one and two years after an episode of DVT are recommended. Complaints, clinical signs of PTS using the Prandoni score for PTS and CEAP score for CVI, and especially pre-tibial edema are to be investigated. In general, DVT patients are instructed to use the MECS for 2 years [55,56]. In retrospect however, about half of the DVT patients do not develop PTS after one year (Figure 4) and do not need wearing MECS [55,56] (Table 2). Consequently, a duplex ultrasound should be performed at 6 months, one year and two years post-DVT, to determine whether there is still a need for wearing MECS and if additional treatment is necessary (Table 2). If no pathologic changes remain (complete recanalization, no reflux the venous system functions normally and no PTS exist or will occur, the MECS do not need to be worn any longer and the asymptomatic patient can be discharged from the follow-up (Table 3). Should reflux of the deep venous system be found, a MECS is prescribed. Patients then visit the outpatient clinic twice a year to evaluate this treatment. When necessary, the superficial venous system is investigated and sanitized [57,58]. If recirculation of blood through the gastrocnemic veins is found, this can also be treated using ultrasound-guided foam sclerocompression therapy. Should problems arise, additional investigation is pursued, including a measurement of the ambulant venous pressure, phlebography, and/or measurement of the pressure measurement in the compartments of the leg. An elevated pressure in one or more compartments of the leg may be treated by fasciotomy.

Patients also should receive guidelines for their daily life, including the advice to engage in daily exercises such as walking, biking, or swimming, or the exercises as described by Junger et al. [67].

Should obstruction of the deep venous system be found, a MECS is prescribed [68]. If this obstruction only involves a small part of the iliac vein, a desobstruction procedure and venous stent placement of the de Palma procedure [69] is discussed with the patients and a phlebography is performed (Figure 5).

Venous ulcers are treated according to modern evidence-based guidelines [70]. Failure of venous ulcer treatment may be a reason to perform the operation according to Schmeller and Roszinski [71], in which an ulcer is tangential excised completely, after which the skin defect is covered with a split-thickness skin graft.

The role of medical elastic stockings MECS in the treatment of PTS

The above described protocol is the so-called Rotterdam approach, and incorporates the evidence-based-diagnostics and treatments available for DVT and PTS (Figure 5). The key element in the symptomatic therapy of PTS is the application of compression to the leg by means of bandages or MECS [57,58,68], but it does not prevent DVT recurrence. Compression therapy is much more effective in an ambulatory versus a sedentary situation because of the interaction of the compression applied to the calf muscles. The pressure applied to the leg (the so-called interface pressure) reduces the volume of blood in the venous system and thus increases the efficiency of the muscle pump function. Incompetent valves may become competent again by the reduction in diameter of the veins to which pressure has been applied.

In compression therapy it is important to find a balance between the three characteristics of the used materials hysteresis, stiffness and the elasticity. Recent research has demonstrated that the stiffness of the materials used in MECS plays an important role in the quality of

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
Varicose veins	None	Few, scattered: branch varicoe veins	Multiple: GS varicose veins confined to calf or thigh	Extensive: thigh and calf or GS and LS distribution
Venous oedema	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
Skin pigmentation	Non or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution(lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Entire lower third of leg or more
No. of active ulcers	0	1	>2	> 2
Active ulceration, duration	None	< 3 cm	> 3 mo, < 1 yr	Not healed > 1 yr
Active ulcer, size	None	< 2 cm diameter	2 to 6 cm diameter	> 6 cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings + elevation

Table 7: The Venous Clinical Severity (VCS) Score system of PTS or CVI [64] GS, greater saphenous; LS, lower saphenous

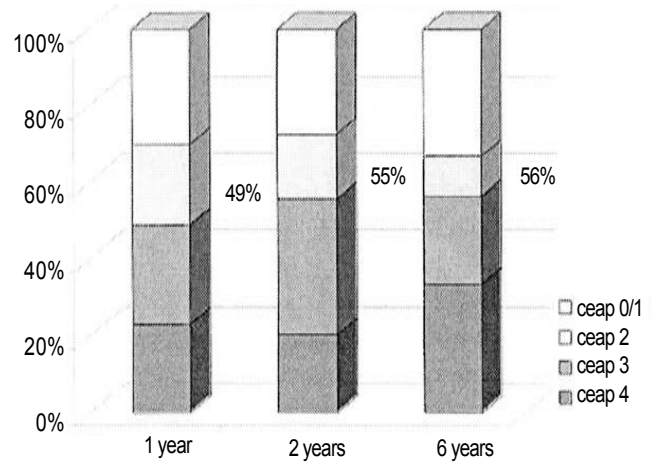


Figure 4: Incidence of DVT patients with the post-thrombotic syndrome (PTS) according to the CEAP classification during long-term follow-up [65]

compression. It appears that the use of stockings with a high dynamic stiffness index is highly effective in reducing the complaints and complications of PTS [72].

Although elastic stockings compression therapy is still the cornerstone in the symptomatic treatment of PTS, but it does not prevent DVT recurrence and the frequency of PTS. Severe reflux often affects all the venous layers and is a main risk factor for DVT recurrence. The volume of reflux can then be reduced significantly by treating the insufficiency of the superficial venous system. Compression therapy will still be necessary thereafter in symptom relief of PTS, given that the insufficiency of the deep venous system will remain. Valve surgery is an attractive theoretical option, but remains an experimental treatment to date.

A desobstruction procedure can be considered eventually, combined with placement of a venous stent if a vein remains obstructed after DVT (Figure 5). This procedure is particularly useful for obstruction of the proximal part of the iliac vein. Finally, an increased ambulatory venous pressure may be treated partially by decompression of the compartment with the vein through fasciotomy.

Proposed Study Design to Bridge the Gap between DVT and PTS

A clinical and basic research study protocol on the influence of the duration of compression therapy in the development of PTS, should be prospectively evaluated by objective measurable parameters. Complaints in PTS range from a mild discomfort to pain, restless legs, pigmentation disorders and finally ulcus cruris venosum, which is considered the terminal symptom of PTS. Despite anticoagulant treatment of DVT, the frequency of ulcus cruris is as high as in the 1970s of the previous century indicating the persistence of a serious social economic problem. The statement by Charpy and Audier (1956) is still very much true today: “the agony of the post-thrombotic patient begins as soon as he/she is –seemingly cured- released from hospital” [73]. The studies of Brandjes et al. [55] and Prandoni et al. [56] have clearly demonstrated that about half of the DVT patient do not develop PTS in the control group, and that compression therapy using medical elastic compression stockings (MECS) decreases this incidence with 50% (from circa 50 to 25% indicating an absolute reduction rate of 25%) during an observation and treatment period of 2 years following DVT. It is unknown what should be done with these symptomatic PTS patients after 2 years. Unfortunately, this evidence-based knowledge is not applied generally in daily practice. Family doctors and internists usually treat the acute phase of DVT with anticoagulants for at least 3 to 6 months, and discontinue anticoagulation without further follow-up or testing for PTS or CVI. Physicians with interest and expertise in phlebology are usually confronted much later and frequently too late with overt post-thrombotic complications of DVT.

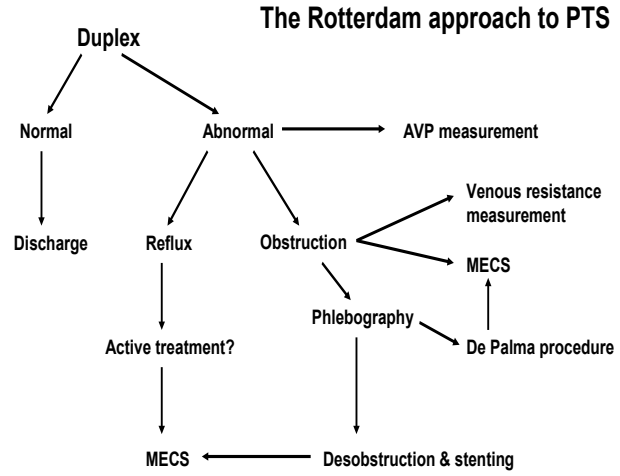


Figure 5: The Rotterdam approach to the post-thrombotic syndrome (PTS).

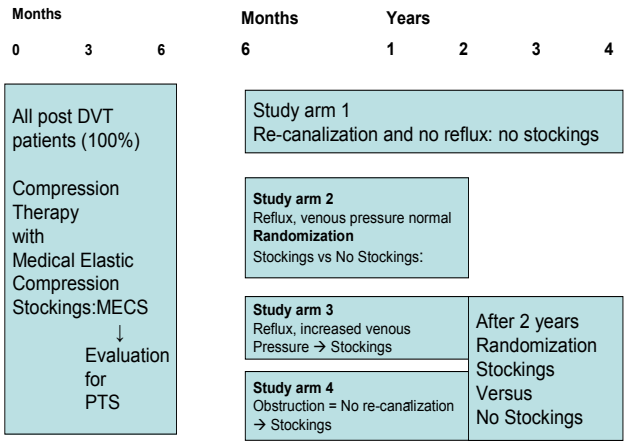


Figure 6: Study design, protocol, time schedule, clinical score assessment and procedures for prospective evaluation of post-DVT VTE-recurrence and PTS with the need of to wear medical elastic stockings (MECS).

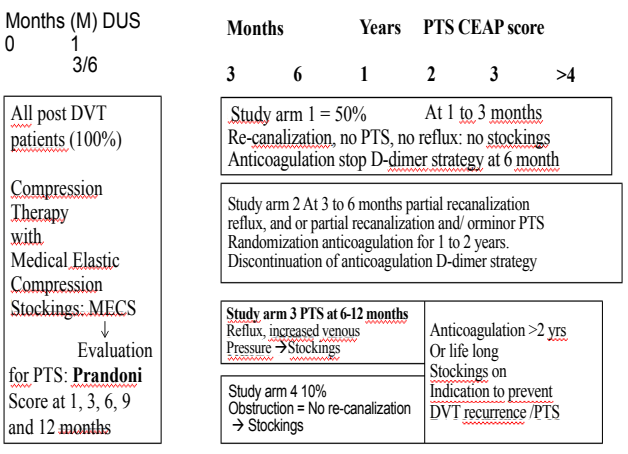
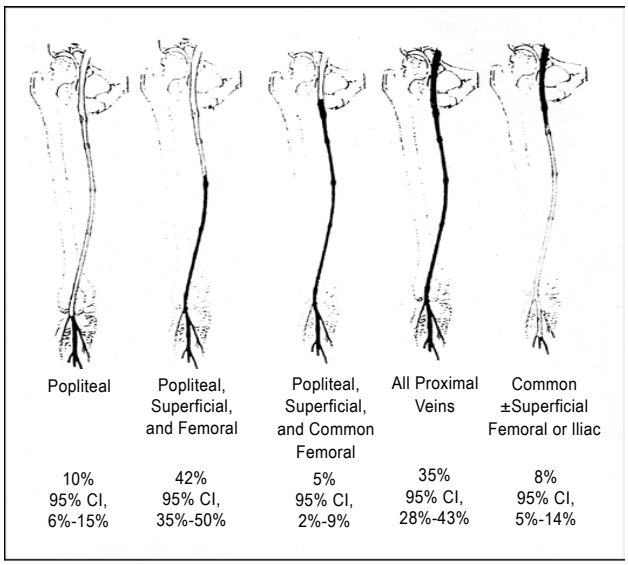


Figure 7 : The Rotterdam Erasmus PTS study design 2013/2014 according to Michiels, Moosdorff and Neumann.



The distribution of proximal venous thrombi in patients with clinically suspected deep vein thrombosis. CI indicates confidence interval.

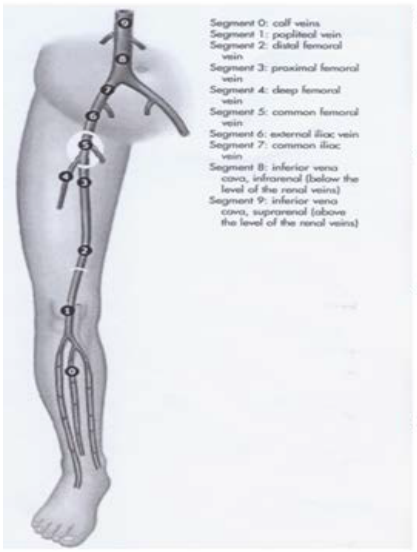
Figure 8: Distribution of proximal deep vein thrombosis (DVT) in 563 patients with DVT on venogram in the popliteal vein, femoral vein and extension into the femoro-iliac vein or as isolated ileo-femoral DVT according to Prandoni et al Arch Int Med 1993;153:2777 : For therapeutic implications see Figures 9 and 10.

There is good evidence from two prospective studies that compression therapy with MECS is highly effective in reducing the frequency of PTS at time point 6 to 9 moths post-DVT [55,56]. In view of this, three interesting and yet unanswered questions in the treatment of DVT are:

1. Which DVT patient has a clear indication for long-term compression therapy for symptom relief of PTS after the initial treatment in the acute phase of DVT?
2. Is 3 months the appropriate point in time to determine by CUS candidates with no RVT and low risk of DVT recurrence versus the presence of RVT and reflux with a high risk of DVT recurrence and PTS
3. Is continuing compression therapy after 2 years effective in the prevention DVT recurrence and reduction of PTS?
4. Which PTS patients needs additional anticoagulant treatment (Table 3)?

Natural History of DVT

The treatment of a patient with DVT is primarily targeted to prevent the acute complications, such as pulmonary embolism, which may even be fatal. In addition, anticoagulant treatment is given to stop thrombus growth. Data from literature clearly indicate that rapid thrombus resolution and full re-canalisation of the vein reduces the chance of damage of the vein walls and valves [47]. This concept indicates the need for a rapid and adequate anticoagulant treatment as soon as the diagnosis DVT is made. Recent studies show that early mobilisation of the patient, adequate anticoagulant therapy and immediate compression treatment with MECS reduces the chance to PTS significantly [75]. There are no data available indicating the time needed to reach final (i.e. maximal or full) re-canalisation. Some authors propose this process takes approximately one year, but most experts agree that after 2 years no further re-canalisation can be



- Class I: calf vein thrombosis
  - Limited to the calf veins
    - Good recanalisation
    - Good outflow/collatenals
    - Low PTS
- Class II: femoro-popliteal thrombosis
  - Popliteal vein, Femoral vein, Deep femoral vein
    - Good recanalisation
    - Good outflow/collatenals
    - Medium PTS: some need for extended anticoagulation, NOAC
- Class III: femoro-iliac thrombosis
  - Common femoral vein, iliac veins
    - Bad recanalisation
    - Impaired outflow/ bad collaterals
    - High PTS: need for extended anticoagulation, NOAC
- Class IV: inferior vena cava thrombosis
  - Inferior vena cava
    - Bad recanalisation
    - Impaired outflow/ bad collaterals/ bilateral
    - High PTS: need for cather directed thrombolysis and extended anticoagulation, NOAC

Figure 9: Standardized Lower Extremity Thrombosis (LET) clasification (Class) of DVT extension and risk on PTS [79]. Courtesy of Dr C. Wittens Vascular Surgeon, University Medial Center, Maastricht

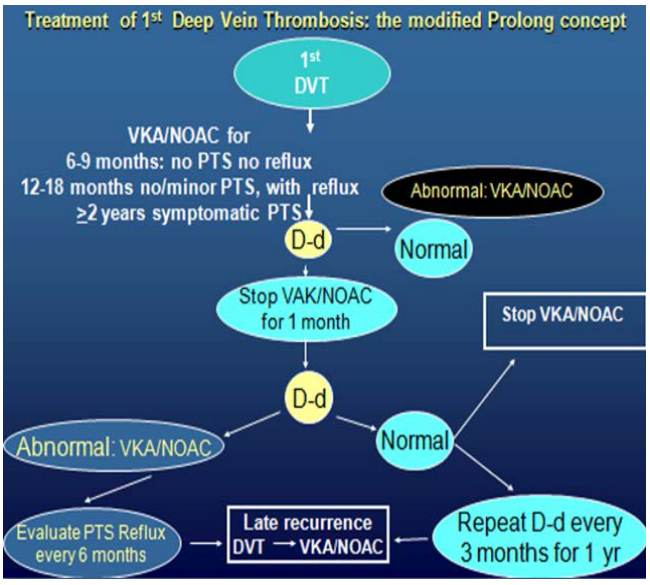


Figure 10: Rotterdam modification of the PROLONG Study Algorithm [54] for the duration and extension of anticoagulant treatment in post-DVT patients on top of objective risk stratification in Table 3 and Figure 7 [74,75].

expected [47,48,50]. It has been demonstrated that rapid and complete recanalisation within 3 months post-DVT is associated with a low DVT recurrence rate and no risk on PTS, whereas delayed and incomplete recanalisation at 3 months post-DVT is associated with reflux and a high risk of DVT recurrence as the cause of PTS or worsening of already existing PTS. This dependes on the severity of DVT and the presence or absence of transient or persistent risk factors for thrombosis recurrence and PTS.

The Post-Thrombotic Syndrome (PTS)

The incidence of PTS in untreated DVT patients is approximately 10-30% [37-39]. Phlebologists generally distinguish two main types of PTS.

1. The reflux type (circa 90%)
2. The obstruction type (circa 10%)

In a substantial number of patients only partial re-canalisation occurs (as opposed to either complete obstruction or complete re-canalisation). Duplex ultrasound imaging can assess this. DVT patients with re-canalisation can be divided in two groups:

1. Those with functional (intact) vein valves
2. Those with dysfunctional vein valves

Dysfunctional vein valves result in reflux in the popliteal and femoral vein (LET Class II, Figure 9). and ultimately in increased venous pressure, which is the main hemodynamic determinant of DVT recurrence and the development of PTS. Patients with rapid and complete recanalisation within 3 to 6 months post-DVT with no reflux and with normal ambulatory venous pressure (AVP) are candidates for discontinuation of medical elsastic stockings (MECS) at 6 months post-DVT (Figure 10).

Diagnostic Work-up of PTS

The diagnostic work-up of post-DVT patients should follow the Rotterdam Approach to PTS in Figure 5.

The Reflux Problem

The physiological return of venous blood from the legs is based on the vis a fronte, the vis a tergo, the venous capacity (tonus), the arteriovenous pulse pump, and muscle pumps, due to the fact that the human heart is a pressure pump instead of a suction pump. Among all these mechanisms the most important are the muscle pumps in the legs. The transport of blood is facilitated mainly by the calf muscle pump, but the muscle groups of the upper leg and thigh also contribute to this transportation. This pump mechanism is based on the presence of valves in the veins, which allows a one-way blood flow when the muscles surrounding it are contracting. Loss of valve function in the popliteal and femoral veins (LET Class III, Figure 9). causes venous reflux and leads to overloading of the venous system, which in turn leads to widening of the veins and finally to an increase in venous

volume. If the venous volume surpasses the capacity of the calf muscle pump, ambulatory venous hypertension results, which in turn cause further distension of the vein, leading to more valvular incompetence and the development of secondary varicose veins. If there is residual obstruction in a vein, venous resistance and pressure increases, which also leads to a higher venous volume and the above-described cascade is repeated. In general, reflux causes more decompensation if it occurs in the popliteal and/or femoral part of the venous system and obstruction causes more decompensation if it occurs more proximally in the ileofemoral vein (Figure 9). PTS is highly influenced by gravity. In the standing position, venous pressure at the ankle will be about 90 mm Hg; during walking, this pressure should decrease to about 20 mmHg.

Venous blood from the legs is pumped back to the heart by different mechanisms of which the "calf muscle pump" during walking is the most important one. The heart is only a pressure pump and not a sucking pump. When reflux is due to the loss of functional vein valves in re-canalised veins as happens in PTS, the muscle pump during walking will be less effective. As long as the capacity of the calf muscle can compensate for the reflux, there will be no visible signs of PTS in the involved leg of the DVT patient. In a number of patients the reflux will decompensate the venous system of the leg after a shorter or longer period following DVT. Decompensation signifies the situation in which the calf muscle pump during walking is insufficient to pump back venous blood to the heart, which will result in an increased venous pressure during walking (increased ambulant pressure or so-called venous hypertension).

The Venous Pressure Problem and Reflux or Obstruction

In physiological conditions, the venous pressure in the legs, while standing (standing venous pressure), is the same for healthy and PTS individuals. The venous valves are opened in standing position. Therefore, the standing venous pressure corresponds with the hydrostatic pressure of the right atrium to the place of measurement in the veins of the lower leg (approximately 80 mm Hg). The ambulant PTS patient, on the contrary, differs from the healthy individual. In healthy individuals, the ambulant venous pressure will decrease to about 15 to 20 mmHg, but will decrease significantly less in PTS patients (AVP measurement in Figure 5). This phenomenon is defined as venous hypertension.

Venous hypertension in PTS patients is responsible for the changes of the microcirculation in the skin of the lower leg. These changes of the microcirculation lead to leakage of water, proteins and erythrocytes which in turn clinically present as oedema, pigmentation, atrophy blanche, dermato- and liposclerosis, chronic compartment syndrome and ulcus cruris venosum. So, all clinical signs of PTS are the result of the disturbed microcirculation induced by the dysfunction of the venous marcocirculation (Figure 3).

The Obstruction Problem

Patients with obstructive PTS often have severe signs of venous insufficiency, for which compression therapy is recommended. The aim of treatment is prevention of complications such as dermato-and liposclerosis, atrophy blanche, stiffness of the ankle joint and ulcus cruris venosum. When occlusion of in the popliteal or femoral veins is present, compression therapy will not always be feasible, because it may compromise the collateral veins too much and impair muscle pump function, resulting in impaired flow of venous blood from the lower leg to the heart. In addition to the pressure problem patients with PTS also suffer from increased venous resistance, which leads to increased ambulatory venous pressure and a longer transmission time of the venous blood. For patients with obstruction of the iliac vein, de-obstructing and stenting the vein may be considered [43]. The long-term results are yet unknown, but most experts recommend additional long-term or even life-long anticoagulant treatment in case this treatment is given.

Type and Duration of the Study

We propose a prospective randomized clinical outcome study with a follow-up period of 4 to 5 years (Figure 6). Patients with DVT at time of diagnosis are included. All DVT patients will according to the standard immediately receive anticoagulant and compression therapy. In case of pronounced edema, compression therapy will consist of short stretch bandages until the edema is relieved. In case of minor edema, compression therapy with MECS will be prescribed. MECS should be "flat knitted" stockings pressure class II and if complicated by edema class III with a high resistance coefficient. Objective documentation will consist of phlebological controls, duplex ultrasound imaging and ambulant venous pressure measurements (when indicated) and will take place at 0, 1, 3, 6, and 12 months (Figure 7) and subsequently every year. Based on these objective measurements and assessments, DVT patients will be risk stratified at 6 months post-DVT for continuation or discontinuation of compression therapy with MECS according to the study design (Figure 6).

Study Design

All DVT patients will be assessed for severity according to the Rotterdam modification of the Wells clinical score assessment at the time of diagnosis and at time of inclusion (Table 1) [15-17].

All DVT patients will be treated immediately with low molecular weight heparin followed by vitamin K antagonist (VKA) for 6 months. This duration of VKA treatment is based on risk stratification according to current recommendations [70].

All DVT patients will be treated immediately with compression therapy (MECS) for 6 months, but should be discontinued as soon as leg swelling has disappeared. Patients with complete recanalisation without reflux and no PTS at time point 3 months post-DVT will discontinue MECS and anticoagulation at 6 months post-DVT, which is predicted to be highly cost-effective

All patients with obstruction on duplex ultrasound imaging (no re-canalisation) will receive compression therapy (MECS) to relief PTS symptoms for 2 years. After 2 years a randomization will take place for continuation and discontinuation of MECS for at least another 2 years.

DVT patients with partial or incomplete re-canalisation at 3 months post-DVT (Figure 3) will be risk stratified and subdivided in those without reflux and those with reflux on duplex ultrasound imaging.

Patients with reflux and increased venous pressure (venous hypertension) will receive compression therapy (MECS) for 2 years. After 2 years randomization will take place for continuation vs. discontinuation of MECS for another 2 years.

Allocation of PTS Patients

Allocation of PTS patients to the study arms follows the concept in Table 3.

Study arm 1

Patients with complete re-canalisation at 3 months, no reflux, and asymptomatic (no PTS) will not continue MECS, stop anticoagulant treatment, and will be remained in follow-up for at least 4 years.

Study arm 2

Patients with reflux but normal venous pressure (no venous

hypertension) and no PTS at 6 months will be randomized for MECS vs no MECS and continuation of anticoagulation for 2 years for 2 years.

Study arm 3

Symptomatic patients (PTS) with partial or complete recanalization but with reflux and increased venous pressure (venous hypertension) will receive compression therapy (MECS) for 2 years. After 2 years randomization will take place for continuation vs. discontinuation of MECS for another 2 years.

Study arm 4

All patients with obstruction on duplex ultrasound imaging (no re-canalisation) will receive compression therapy (MECS) for 2 years. After 2 years a randomization will take place for continuation and discontinuation of MECS for at least another 2 years.

PTS patients in study arm 3 and 4 are to be treated according to the PROLONG PLUS study if indicated according to the concept in Table 3.

Evaluation Procedures

At time of inclusion 1 month and 3 months after DVT

Evaluation of clinical findings and details of positive echogram for DVT from the records of various center where the diagnosis of DVT was made blood collection (plasma, serum and DNA samples in deep freezer) for risk factor evaluation in retrospect.

Evaluation at time points 1 month, 3 and 6 months, 1 year, and 2 years post-DVT

1. Complete analysis for PTS according to Prandoni and for CVI according to CEAP.

2. CUS colour at 1, 3 and 6 months for assessment of the degree of recanilization, reflux and obstruction

3. Allocation of PTS patients at 6 months to each of the four study arms.

4. At time point 2 years randomization of PTS patients arm 3 and 4 into MECS versus no MECS with the exception of those who need active treatment for PTS based on objective measurements.

5. Repeat all measurements for PTS according to Prandoni, for CVI according to the CEAP classification, and for assessment of the degree of recanalization, reflux and obstruction by CUS and colour Doppler at 9, 12, 18 and 24 months during follow-up.

Real life documentation of post-DVT patients and the need of wearing stockings and the duration of anticoagulation

All DVT patients will be treated immediately with low molecular weight heparin followed by vitamin K antagonist (VKA) for 6 months. This duration of VKA treatment is based on risk stratification according to current recommendations (70). All DVT patients will undergo a complete evaluation for PTS at 3 and 6 months post-DVT. Four types of PTS at 3 months post-DVT are distinguished depending on objective measurement criteria for PTS (Table 2) and allocated to the four study arms of the study design (Figure 6). DVT patients with partial or incomplete recanalisation of veins at 3 and 6 months post-DVT will be risk stratified and subdivided in those without reflux and those with reflux on duplex ultrasound imaging. DVT patients with no re-canalization (obstruction) at 6 months will undergo invasive testing according to the Rotterdam approach.

The diagnostic work-up of post-DVT patients should follow the Rotterdam Approach to PTS according to Neumann for the indication wearing stockings in (Figure 7) [74,75]. To address these questions, we propose a prospective randomized clinical outcome study with a follow-up period of 1 to 2 years (Figure 7). Patients with DVT at time of diagnosis are included. All DVT patients will according to the standard immediately receive anticoagulant and compression therapy. In case of pronounced edema, compression therapy will consist of short stretch bandages until the edema is relieved. In case of minor edema, compression therapy with MECS will be prescribed. MECS should be "flat knitted" stockings pressure class II and if complicated by edema class III with a high resistance coefficient. Objective documentation will consist of PTS score assessment and duplex ultrasound imaging (plus ambulant venous pressure measurements when indicated at time of making a therapeutic decision) will take place at 1, 3, 6, 9 and 12 months (Figure 7) and subsequently every year. Based on these objective measurements and assessments of PTS, DVT patients will be risk stratified at 3 months post-DVT for continuation or discontinuation of compression therapy with MECS and anticoagulation according to the study design (Figure 7) followed by discontinuation when no evidence of relux obstruction or PTS symptoms are present.

Palareti et al. and other studies showed that normal versus increased D-dimer levels one month after discontinuation of regular anticoagulation is associated with an incidence DVT recurrence of about 5% patient-years and 10 to 15% patient/years respectively [54]. This difference was independent from other factors like thrombophilia or or the transient or persistent presence of delayed recanaliszation with RVT and/or reflux at and after 3 months post-DVT. Such post-DVT patients with increased sensitive D-dimer after discontinuation surely belong to the group of symptomatic post- DVT patients at high risk to develop DVT recurrence as the cause of PTS or worsening of the already existing PTS symptoms. (score > 3, Table 3 integrated in the algorithm in (Figures 7 and 8) [54,74-76]. In the PROLONG study, extended anticoagulation in post-DVT patients with increased D-dimer reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer on month after discontinuation of regular anticoagulation [76]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer very likely do occur in those with incomplete or complete RVO after 3 months with reflux score 3 or more (Table 3). This important observation has been confirmed by Latella et al [78] in a prospective study of 305 DVT patients selected for quatitative ELISA D-dimer (VIDAS) measurement 4 months post-DVT. Of these 305 46% developed PTS (mild 25%, modeate 13%, severe 7%) and 54% did not during 24 months follow-up. Mean D-dimer level measured 4 months post-DVT were significantly higher in patients with PTS vs without PTS (712 vs 444 ug/L P= 0.02). At time of D-dimer measurement 213 were taken anticoagulans. The PROLONG study [54] demonstrated the need to continue anticoagulant treatment in post-DVT patients with increased D-dimer level during anticoagulant treatment and when D-dimer levels are above the upper level of normal one month after discontinuation of anticoagulation treatment (Figures 7 and 8) [74-76].

Conclusion

As the extension of the PROLONG study Palareti performed the DULCIS (D-dimer and ultrasound in combination Italian Study) to establish the optimal duration of anticoagulation for VTE in 988 evaluable DVT patients with a first unprovoked DVT [77]. After at least 3 months of anticoagulation D-dimer was measured and DUS

performed to measure residual venous thrombosis (RVT <4mm) and followed according two main strategies. First, if the D-dimer level was below age and gender specific cut-off for each of the different D-dimer assay used, antiocoagulation was stopped and D-dimer levels were reassessed at 15, 30, 60 and 90 days [51]. If at time of at least 6 months post-DVT the D-dimer remained below the cut-off, anticoagulation was definitely stopped and patients were followed up for 2 years. In the cohort 109 post-DVT patients with at least one D-dimer measurement above cut-off, who refused oral anticoagulation treatment the incidence of major VTE was 8.8%, and distal DVT or SVT 2.3% patient/years. In 506 (51%) of the 988 analyzed patients all D-dimer were below the cut-off in the 3 months (90 days) after stopping anticoagulation. The incidence of VTE was 2.8%, distal DVT 1.1% and superficial venous thrombosis (SVT) in 2.3% patient/years [51]. Second, if one of the D-dimer levels was above the cut-off in the period of 3 month (90 days) after discontinuation anticoagulation was resumed. This cohort 373 patients with increased D-dimer levels above the age and gender adjusted cut-off levels received oral anticoagulation for 2 years follow-up and only 4 VTE events (0.7% patient/years) were observed at the cost of 14 major bleedings (2.3% patients/years) [51]. These data may indicate that the upper limit of a normal D-dimer test in post-DVT patients with early PTS seem not low enough for safe DVT recurrence prevention [77].

The distribution of proximal deep vein thrombosis (DVT) in 563 patients with DVT on venogram in the popliteal vein, femoral vein and extension into the femoro-iliac vein or as isolated ileo-femoral DVT according to Prandoni are shown in Figure 8 [78]. Arnoldussen, Toonder and Wittens proposed in 2012 a novel scoring system for lower extremity venous thrombosis extenesion (LET) on complete CUS. The LET score can be used to expand and standardize the documentation of DVT localization and extension, to help identify optimal treatment options in patients with acute DVT in both the clinical and research setting (Figure 9) [79]. The present review produced good evidence that recanalization of distal DVT in the calf and lower popliteal region is predicted to be rapid and complete with no reflux on DUS and no or very low risk on PTS (Figure 9) obviating the need of wearing stockings and no need for extended anicoagulation (Figure 10). When the re-canalisation of the popliteal-femoral region is incomplete at 3 to months post-DVT with the presence of reflux due to valve destruction irrespective of the degree of recanalization on CUS, this is associated with a high risk of DVT recurrence and symptomatic PTS (Figure 9) indicating the need to wear MECS and extended anticoagulation (Figure 10) preferentially with low dose of novel oral anticoagulants (NOAC) [75,80]. Patients with acute ileofemoral and extension of proximal DVT into the ileofemoral region (LET Class III and IV, Figures 9 and 10) are candidates for catheter directed thrombolysis as the risk of severe post-thrombotic syndrome by anticoagulation alone is irreversible and high [80-82].

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