

Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014

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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 mo follow-up. Compression ultrasonography (CUS) of the leg veins has a negative predictive value (NPV) of 97%-98% indicating the need of repeated CUS testing within one week. A negative ELISA VIDAS safely excludes DVT and VTE with a NPV between 99% and 100% at a low clinical score of zero. The combination of low clinical score and a less sensitive D-dimer test (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 mo and no reflux is associated with a low or no risk of PTS obviating the need of MECS 6 mo after DVT. Partial and complete recanalization after 3 to more than 6 mo is usually complicated by reflux due to valve destruction and symptomatic PTS. Reflux seems to be a main determinant for PTS and 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 mo 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 mo post-DVT. The presence or absence of RVT but with reflux at 3 to 6 mo 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 postthrombotic syndrome (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 mo 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?

Key words: Deep Venous thrombosis; Ultrasonography; Post-thrombotic syndrome; ELISA VIDAS D-dimer; Medical elastic stockings; Anticoagulation

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Core tip: A novel clinical concept for the assessment of acute deep vein thrombosis (DVT) and the post-thrombotic syndrome (PTS) by DUS in routine clinical practice at 1, 3 to 6 mo and at one year post-DVT will separate post-DVT patients in 4 groups: Group 1: rapid complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and medical elastic compression stockings (MECS) can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS at 6 months post-DVT when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

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DEEP-VEIN THROMBOSIS

The sequential use of compression ultrasonography (CUS), a sensitive ELISA VIDAS D-dimer test and clinical score to rule in and out deep vein thrombosis (DVT) and alternative diagnosis (AD) is safe and cost-effective (Figure 1)^[1-10]. The general application of DVT exclusion by a negative SimpliRed (Simplify) and low clinical score is not safe enough^[5,9]. After a first negative CUS the prevalence of DVT is uniformly low, 2%-3%^[8,9-14]. The combination of a first negative CUS and a D-dimer level of ELISA VIDAS < 1000, Tinaquant < 800 µg/mL or negative SimpliRed (Simplify) will exclude deep vein thrombosis with a NPV of

more than 99% in 4 prospective outcome studies (Figure 1)^[9,11-13]. A moderate to high probability in combination with a increased ELISA D-dimer (VIDAS > 1000 or Tinaquant > 800 µg/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 (Figure 1)^[8,9,11-14].

DEEP VEIN THROMBOSIS AND THE POST-THROMBOTIC SYNDROME

Recanalization of distal DVT is frequently rapid and complete within one to three months without reflux and no or low risk of post-thrombotic syndrome (PTS) in an asymptomatic leg obviating the need to extend anticoagulation at 6 mo post-DVT. Recanalization of proximal DVT is more frequently delayed and may be completed after 3, 6 to 9 mo post-DVT with a high incidence of reflux, DVT recurrence and PTS (Figure 2)^[15-17]. 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 the post-thrombotic syndrome (PTS)^[15,16]. 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 2-2 cm of the greater saphenous vein (GSV). Among the calf veins, the 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*^[15] studied the relationship between complete recanalization (lysis time) and the development of reflux in patients with a first episode of DVT at 3 mo interval during the first year (Figure 2). 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 compressible venous segment. Complete lysis of the leg vein clot (recanalization) was presumed to have occurred when spontaneous phasic flow returned and the vein was completely compressible^[15]. For the PTVs, flow detected after distal augmentation in a completely compressible vein is accepted as evidence of complete recanalization (lysis of the leg vein clot). The median

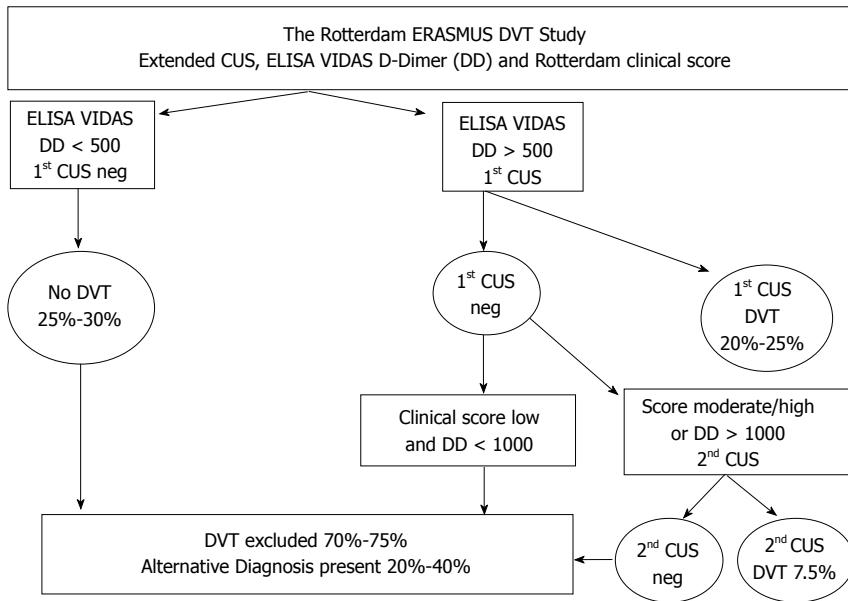


Figure 1 Rotterdam approach to safely exclude and diagnose deep vein thrombosis^[8,9]. CUS: Compression ultrasonography; DVT: Deep vein thrombosis.

Table 1 Scoring system according to Brandjes for mild-to-moderate and severe postthrombotic syndrome^[24]

Subjective criteria			
Symptoms	Score	Signs	Score
For mild-to-moderate PTS: score > 3 of subjective and objective criteria			
Spontaneous pain in calf	1	Calf circumference ↑ by 1 cm	1
Spontaneous pain in thigh	1	Ankle circumference ↑ by 1 cm	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			
Spontaneous pain	1	Calf circumference ↑ by 1 cm	1
Pain on standing/walking	1	Pigmentation, discolouration, and venectasia	1
Edema calf			
Impairment of daily activities	4	Healed or active ulcer	1

time from DVT to complete recanalization (lysis time) was about 3 mo (100 d) for patients without reflux in all segments (Figure 2). In contrast, the median time from DVT to complete recanalization (lysis time) of all segments was about 9 to 12 mo (more than 6 mo) for DVT patients who developed reflux as the main determinant of PTS (Figure 2). In the study of 123 legs with DVT (107 patients) by Markel *et al.*^[16] about two third of the involved legs had developed valve incompetence. 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 posterior popliteal vein, 18%. Reflux appeared to be more frequent in the segments

previously affected by DVT^[16].

From these two prospective clinical research studies^[15,16] it may be concluded that complete recanalization within 3 mo and no reflux is associated with a low or no risk of PTS obviating the need of medical elastic compression stockings (MECS) 6 mo after DVT. On the other hand, partial and complete recanalization after 6-12 mo is frequently complicated by reflux due to valve destruction. Consequently, reflux seems to be a main determinant for PTS and 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^[18,19]. In a prospective outcome study, RVT at 3 mo post-DVT was absent in 30%, which was associated with low recurrence of DVT (1.2% patient/years) during two years follow-up (Figure 3)^[18]. The presence of RVT at 3 mo post-DVT was associated with a DVT recurrence rate of 27% during two years follow-up after discontinuation of anticoagulant treatment (Figure 3)^[18]. The proportion of provoked vs unprovoked DVT was 64% and 36% in patients with complete recanalization within 3 mo and 23% vs 77% in the patient with RVT (incomplete recanalization) at 3 mo post-DVT indicating that the distinction provoked vs unprovoked DVT is artificial in terms of risk on DVT recurrence.

In a previous prospective study of 313 consecutive DVT patients, Prandoni *et al.*^[19] have shown that RVT at any time post-DVT is a risk factor for recurrent VTE. In this study, CUS of the common femoral and popliteal veins was performed at 3, 6, 12, 24 and 36 mo post DVT. The cumulative incidence of normal CUS (no RVT) was 39%, 58%, 69% and 74% at 6, 12, 24 and 36 mo post DVT respectively.

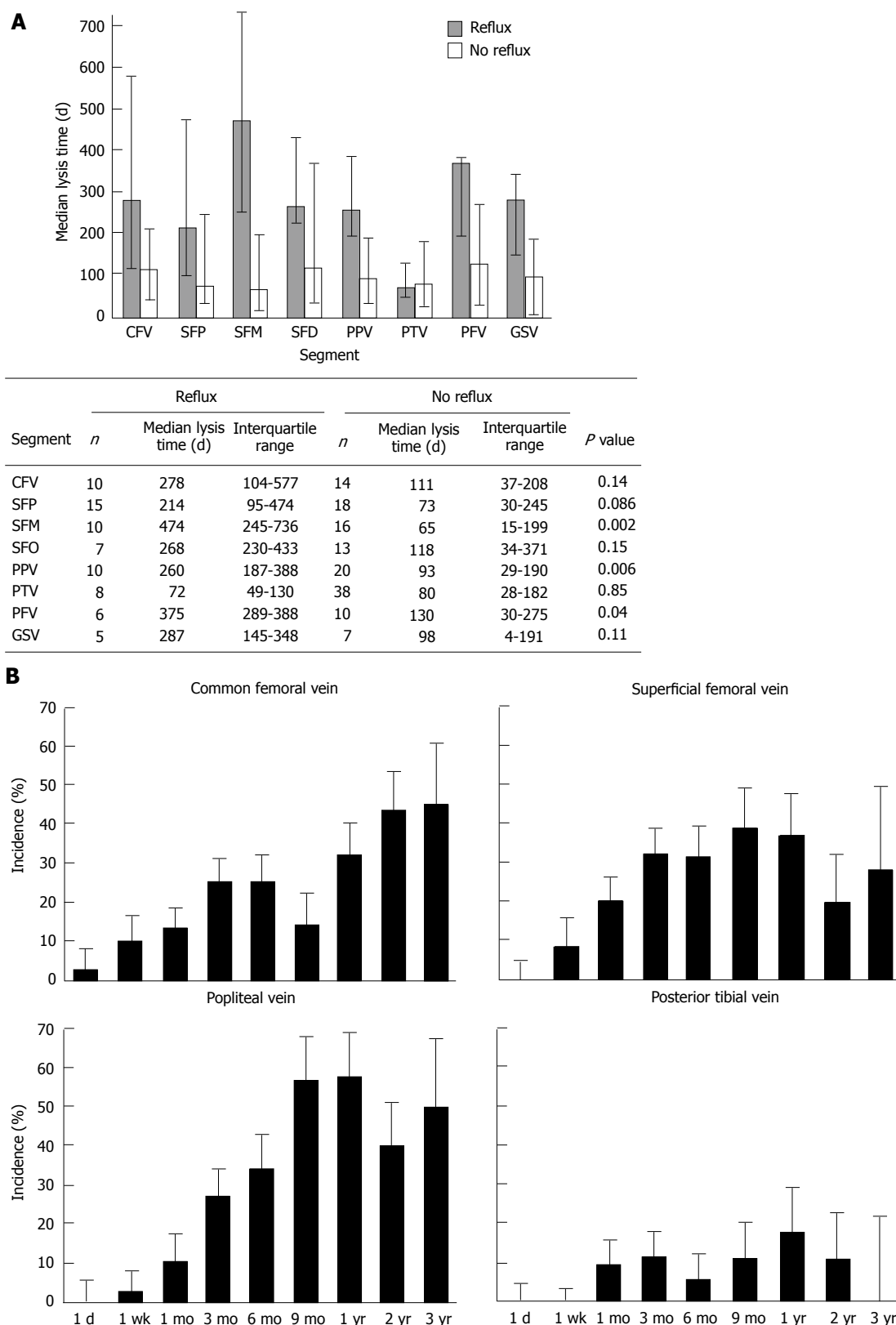


Figure 2 Recanalization of proximal deep vein thrombosis is usually delayed and may be completed after 3, 6 to 9 mo post-deep vein thrombosis with a high incidence of reflux, deep vein thrombosis recurrence and PTS. A: The relationship between the time of complete recanalization after deep vein thrombosis (DVT) (lysis time of leg vein thrombosis) appears to be 3 mo for those DVT patients who did not develop reflux, but appeared to be about 9 to 12 mo for those DVT patients who developed reflux as a main determinant for the development of PTS [Common femoral vein (CFV), superficial femoral vein (SFV), middle superficial femoral vein (SFM), distal superficial vein (SFD), popliteal vein (PPT), posterior tibial vein (PTV), greater saphena vein (GSV)]^[15]; B: Localization of reflux in patients with delayed recanalization (Figure 2A) of deep vein thrombosis^[15].

Of 58 VTE recurrent episodes, 41 occurred at time of RVT. The hazard ratio for recurrent VTE was 2.4 with

persistent RVT vs those with earlier complete vein recanalization^[19].

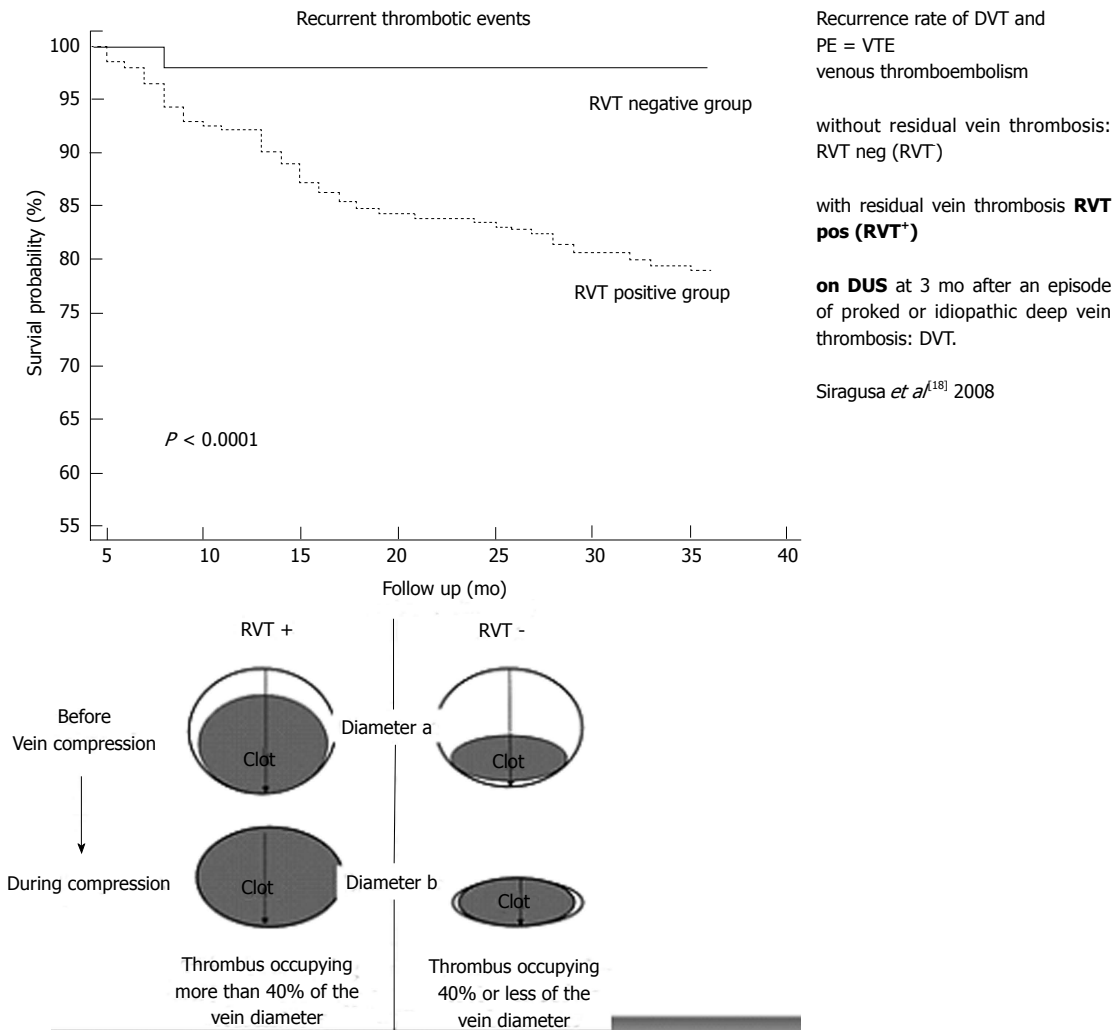


Figure 3 Event free recurrence rate of venous thromboembolism in 78 "low risk" DVT patients with no residual vein thrombosis at 3 mo post-DVT (RVT Neg) as compared to 92 "high risk" DVT patients with RVT at 3 mo post-DVT (RVT Pos group) after discontinuation of anticoagulation during 2 years follow-up in the prospective study of Siragusa *et al.*^[18]. RVT: Residual vein thrombosis.

SCORING SYSTEMS FOR PTS

The fundamental pathophysiologic disturbance with severe leg symptoms or sign after distal and proximal DVT is sustained venous hypertension (Figure 4), which can be measured with invasive venous pressure measurement [ambulant venous pressure (AVP, Figure 5)]. 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.

Identification of no, early and late PTS in patients after a first or recurrent DVT is not reflected by the clinical, etiological, anatomical and pathological (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 PTS exist. Most scoring systems for PTS are based on the

Table 2 Scoring system according to Prandoni for the assessment of post-thrombotic syndrome in the early period 3 to 12 mo post-DVT known as the Vilalta score^[29-31]

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(Vilalta)	
Absent	Score < 4
Mild-to-moderate	core between 5 and 14 at 2 consecutive visits
Severe	score > 15 at 2 consecutive occasions or ulcer at 1 occasion

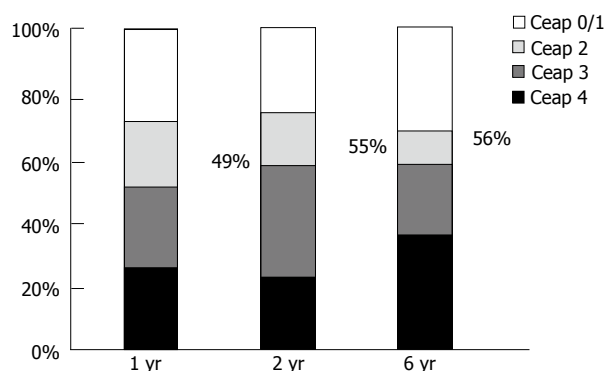


Figure 4 Incidence of the post-thrombotic syndrome according to the CEAP classification in patients with deep vein thrombosis during long-term follow-up^[32].

Table 3 Clinical-etiology-anatomic-pathophysiologic classification for severity of chronic venous insufficiency^[26]

Classification	Symptom
C0 (C = Clinical)	No visible varicose veins
C1	Spider or reticular veins
C2	Varicose veins
C3	Oedema
C4a	Pigmentation 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
Clinical symptoms	Post-DVT
E = Etiology	Deep, perforator, or superficial vein, alone or in combination
A = Anatomic distribution	Reflux or obstruction, alone or in combination
P = Pathophysiologic dysfunction	

Table 4 Widmer classification for assessment of chronic venous insufficiency^[27]

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

presence or absence clinical signs and symptoms during the first year post-DVT and typical signs of chronic venous insufficiency (CVI) one or few years later (Tables 1-5, Figure 5). At least five definitions for early and/or late PTS 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

Table 5 Venous clinical severity score system of PTS or chronic venous insufficiency^[28]

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 varicose 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	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 mo	> 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

GS: Greater saphenous; LS: Lesser saphenous.

by additional objective tools including residual vein thrombosis (RVT) on DUS, and reflux and/or obstruction on color ultrasonography (Table 6)^[18-25]. 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 *et al.*^[24] and by Prandoni *et al.*^[25] (known as the Villalta score^[25-28]) 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 1-5^[29-31].

Two classifications for early PTS have been used by

Table 6 2008 Rotterdam objective scoring system for grading the severity of PTS during the first two years post-DVT based on prospective studies^[18-25]: therapeutic implications

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

ACT: Anticoagulant treatment.

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 1)^[24]. The Brandjes scoring system defined mild-to-moderate PTS as score 3 or more including one objective criterion. Severe PTS is assessed separately and consists of a score of 4 or more (Table 1). 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 (Table 2), and validated his scoring system in prospective studies^[29-31].

Three classifications for PTS have been used by dermatologists and phlebologist the CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) (Table 3)^[26] Widmer *et al.*^[27] (Table 4) and the venous clinical severity (VCS) score (Table 5)^[28]. Clinical symptoms of PTS occurs in about half of the patients within one year post-DVT. A Dutch study prospectively evaluated the incidence and severity of PTS in 93 DVT patients under careful clinical survey using the CEAP classification and confirmed previous studies that half of DVT patients do develop PTS (Figure 4)^[32]. 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).

PREVENTION OF DVT RECURRENCE AND PTS

The incidence of DVT recurrence in the PROLONG and other studies in post-DVT patients with normal vs increased simplify D-dimer levels one month after anticoagulation discontinuation was about 5% pt-years and 10%-5% pt/years respectively^[20-22]. This difference was inadequately interpreted as independent from other factors like thrombophilia or residual venous occlusion. 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 simplify D-dimer^[23]. These data has to be interpreted in view of two other key observations: first the incidence of DVT recurrence after complete recanalization within 3 mo and no reflux is very low^[15,16,18]. Second the incidence of PTS in the control arm of two randomized clinical trials was about 50% within 6 mo and did not significantly increase thereafter, whereas MECS seems to decrease the incidence of PTS from around 50%-25% after 6 to 9 mo follow-up^[24,25]. 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 6 mo with reflux. The hypothesis in Table 6 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.

Patients with provoked and unprovoked DVT at time of diagnosis should be included in prospective studies on bridging the gap between DVT and PTS. All acute DVT patients are instructed to use medical elastic stockings for at least 1 to 3 or 6 mo (Figures 6 and 7). All DVT patients should be followed up by the combine use of the Prandoni (Villalta) score and CEAP assessment for PTS at 1, 3, 6, 9 and 12 mo post-DVT. Patients with acute DVT should be followed up by CUS for the degree of recanalization and PTS symptoms at 1, 3, and 6 mo post-DVT. About one third to half of the DVT patients do not develop PTS at 3 to 6 mo post-DVT and do not need to wear medical elastic compression stockings (Study arm 1 Figures 6 and 7)^[33]. Rapid and complete recanalization of DVT with no residual vein thrombosis (RVT) at 3 mo post-dVT is followed by a very low risk of DVT recurrence after anticoagulant discontinuation (study arm 1, Figures 6 and 7), whereas a delayed recanalization of DVT with RVT at 3 mo post-DVT is associated with a high risk on

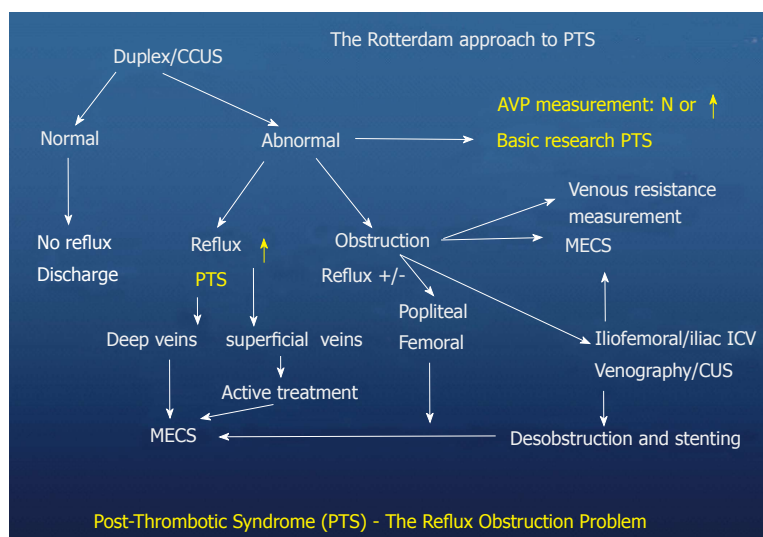


Figure 5 Rotterdam approach to the post-thrombotic syndrome according to Wentel *et al*^[33]. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

Erasmus study: DVT and PTS *vs* MECS or not

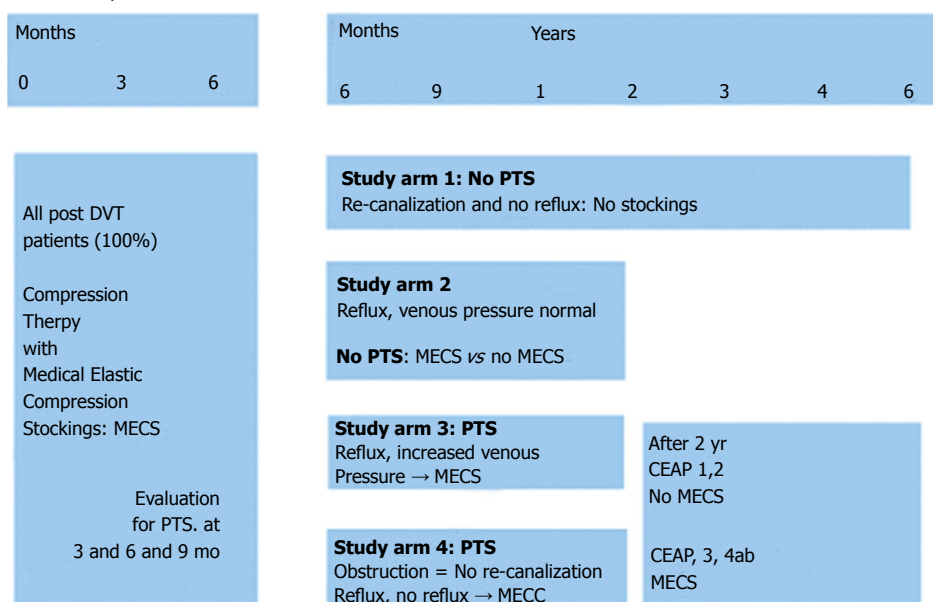


Figure 6 2007 Rotterdam Erasmus study design, time schedule, clinical score assessment and procedures for prospective evaluation of post-DVT venous thromboembolism-recurrence and postthrombotic syndrome. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

DVT recurrence and PTS (Study arm 2, Figures 6 and 7). If no pathological changes on DUS with complete recanalization, no reflux and no PTS at 3 to 9 mo post-DVT it is predicted that DVT recurrence rate and PTS remain low after anticoagulation discontinuation. Patients with PTS according to the Prandoni (Villalta) score and/or CEAP assessment at 6, 9 and 12 mo post-DVT are candidates for continuation to wear MECS and the need to prolong anticoagulation for at least 24 mo to several years (Study arms 3 and 4, Figures 6 and 7).

ERASMUS STUDY DESIGNS TO PREVENT DVT RECURRENCE AND PTS WITH MECS

Study arm 1

Post-DVT patients with complete re-canalisation at

3 mo, no reflux, and asymptomatic (no PTS) will discontinue MECS and anticoagulant treatment (Figure 6).

Study arm 2

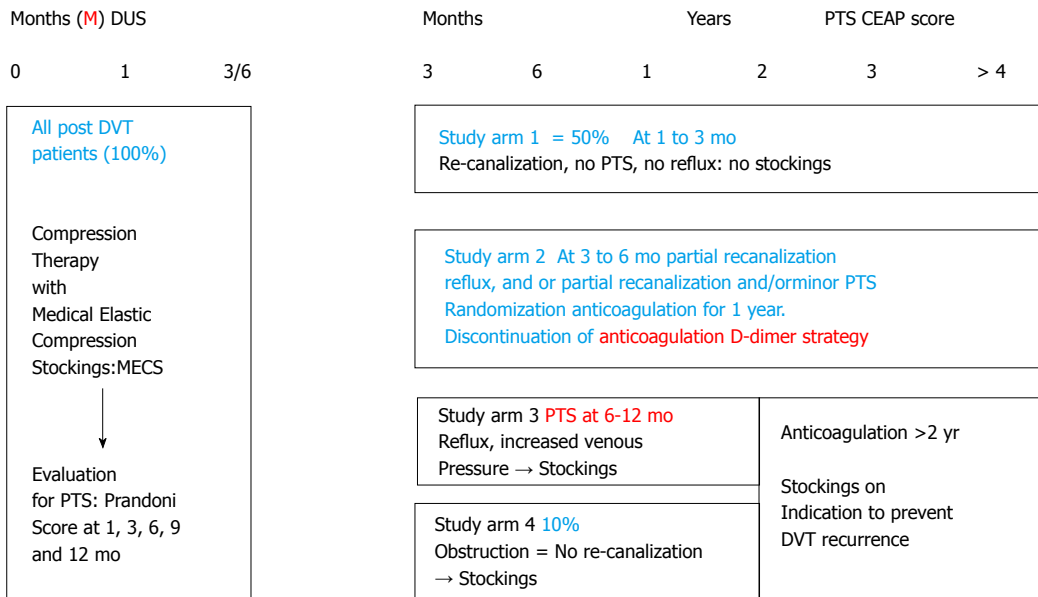
Post-DVT patients with reflux and no PTS will be randomized for MECS *vs* no MECS to address the question whether MECS is needed.

Study arm 3

MECS is recommended in symptomatic (PTS patients with delayed recanalization, reflux and increased ambulatory venous pressure for 2 years followed by randomization between continuation *vs* discontinuation of MECS for another 2 years.

Study arm 4

PTS patients with obstruction are candidates for



The Rotterdam Erasmus PTS study design 2014 Michiels, Strijkers, and Wittens

Figure 7 European DVT - postthrombotic syndrome Bridging the Gap study design 2014. MECS: Medical elastic compression stockings.

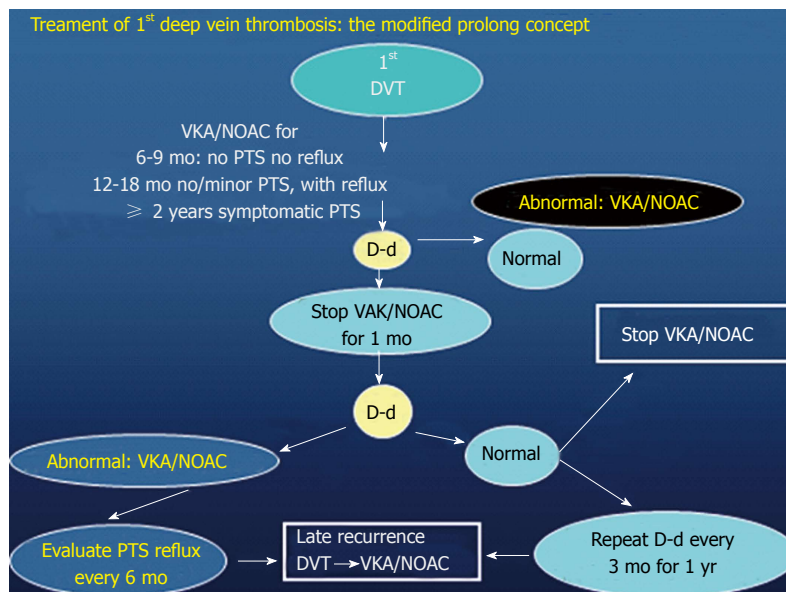


Figure 8 Algorithm modification of the D-dimer strategy according to the modified PROLONG study 23 for the duration and extension of anticoagulant treatment in post-DVT patients on top of objective risk stratification in Figure 7.

MECS for 2 years followed by randomization between continuation and discontinuation of MECS for at least another 2 years.

PTS patients in study arm 3 and 4 are in need for extended anticoagulation for at least 2 to several years according to the PROLONG study (Figures 7 and 8).

Evaluation procedures

At time of inclusion 1 mo and 3 mo after DVT:

Evaluation of clinical findings and details of positive echogram for DVT from the records of various hospitals or medical diagnostic centers 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 mo, 3 mo and 6 mo, 1 year, and 2 years post-DVT:

(1) complete analysis for PTS according to subjective Prandoni (Villalta) score and according to objective CEAP score; (2) DUS colour at 1, 3 and 6 mo for assessment of the degree of recanalization, reflux and obstruction; (3) allocation of PTS patients at 6 mo to each of the four study arms; (4) randomization of study arm 2 at time point 6 mo into no MECS versus MECS; (5) at time point 2 years randomization of PTS patients arm 3 and 4 into MECS versus no MECS; and (6) repeat all measurements for PTS according to subjective Prandoni (Villalta) score, and CEAP classification, and assess the degree of recanalization, reflux and obstruction by DUS and colour Doppler at 9, 12, 18 and 24 mo during follow-up.

Real life documentation of DVT patients and the need of extended anticoagulation: All patients with provoked and unprovoked DVT will be treated immediately with Novel Oral Anticoagulants (NOACs) for 6 mo (Figures 7 and 8) and will undergo a complete evaluation for PTS at 3 and 6 mo post-DVT. Four groups of PTS at 6 mo post-DVT are distinguished depending on objective measurement criteria for PTS (Table 2) and allocated to the four study arms of the study design (Figures 6 and 7). Group 1: rapid and complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and MECS can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS at 6 mo post-DVT when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

Palareti *et al*^[20] and other studies showed that normal versus increased simplify D-dimer levels one month after anticoagulation discontinuation is related to a low versus high DVT recurrence rate of 5% patient-years vs 10%-15% patient/years respectively^[20-23]. Such post-DVT patients with increased insensitive simplify D-dimer after discontinuation surely belong to the group of symptomatic post-DVT patients at high risk to develop PTS (score ≥ 3 , Table 6 integrated in the algorithm in Figures 7 and 8)^[23,35]. In the PROLONG study, extended anticoagulation in post-DVT patients with increased D-dimer above the upper limit of normal will 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 simplify D-dimer on month after discontinuation of regular anticoagulation^[23,34]. This may implicate that DVT recurrence in those patients with either a normal or increased simplify D-dimer very likely do occur in those with incomplete or complete recanalization of the leg veins after 6 mo with reflux score 3 or more (Table 6). This important observation has been confirmed by Latella *et al*^[35] in a prospective study of 305 DVT patients selected for quantitative ELISA D-dimer (VIDAS) measurement 4 mo post-DVT. Of these 305 (46%) developed PTS (mild 25%, moderate 13%, severe 7%) and 54% did not during 24 mo follow-up. Mean ELISA VIDAS D-dimer level measured 4 mo post-DVT were significantly higher in patients with PTS vs without PTS (712 vs 444 $\mu\text{g/L}$ $P = 0.02$)^[35]. At time of ELISA D-dimer measurement 213 were taken anticoagulants. The PROLONG study^[23] 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 anticoagulant treatment (Figures 7 and 8)^[34,35].

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