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 separates 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 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)\(^\text{[1-10]}\). The general application of DVT exclusion by a negative SimpliRed (Simplify) and low clinical score is not safe enough\(^\text{[5,9]}\). After a first negative CUS the prevalence of DVT is uniformly low, 2%-3\%\(^\text{[8,9,11-14]}\). 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)\(^\text{[8,9,11-14]}\). A moderate to high probability in combination with an 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\(^\text{[12,13]}\) to detect a thrombus in about 3% of patients (Figure 1)\(^\text{[8,9,11-14]}\).

**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)\(^\text{[15-17]}\). Loss of valve competence leading to ambulatory venous hypertension (AVH) 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)\(^\text{[15,16]}\). 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\(^\text{[15]}\) 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\(^\text{[15]}\). 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
The Rotterdam ERASMUS DVT Study
Extended CUS, ELISA VIDAS D-Dimer (DD) and Rotterdam clinical score

Figure 1 Rotterdam approach to safely exclude and diagnose deep vein thrombosis. CUS: Compression ultrasonography; DVT: Deep vein thrombosis.

Table 1 Scoring system according to Brandjes for mild-to-moderate and severe postthrombotic syndrome

| Subjective criteria | Score | Signs | Score |
|---------------------|-------|-------|-------|
| Spontaneous pain in calf | 1 | Calf circumference ↑ by 1 cm | 1 |
| Spontaneous pain in thighs | 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 varicosities | 1 |
| Heaviness of foot/leg | 1 | Phlebitis | 1 |
| Impairment of daily activities | 4 | Healed or active ulcer | 1 |

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 thighs 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 varicosities 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, discoloration, and venectasia 1
Edema of foot/calf 1 Pigmentation, discoloration, and venectasia 1
Impairment of daily activities 4 Healed or active ulcer 1

Previously affected by DVT. From these two 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 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. 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). 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). 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. 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.
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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 (PPV), 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\[19\].
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                        |
| Parasthesia               | 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 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.
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 (Table 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 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.[28-31]

Two classifications for early PTS have been used by

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**Table 3 Clinical- etiology-anatomic-pathophysiologic classification for severity of chronic venous insufficiency**[29]

| Classification | Symptom |
|----------------|---------|
| CD (C = Clinical) | No visible varicose veins |
| CI | Spider or reticular veins |
| C2 | Varicose veins |
| C3 | Oedema |
| C4a | Pigmentation or eczema |
| C4b | Lipodermatosclerosis or atrophie blanche |
| CS | 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 |
| A | Anatomic distribution |
| P | Pathophysiologic dysfunction |

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

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

**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 use of analgesics | Daily, severe activity limitation, requiring regular use of analgesics |
| Varicose veins | None | Few, scattered: branch varicose veins confined to calf or thigh | 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 to area and old (brown) | Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple) | Extensive: more than half of lower leg or entire lower limb |
| 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 (cm) | None | < 3 cm | > 3 cm, < 1 yr | Not healed > 1 yr |
| Active ulcer, size (cm) | None | < 2 cm diameter intermittent use of stockings | 2 to 6 cm diameter wears stockings most days | > 6 cm diameter full compliance: stockings + elevation |
| Compressive therapy | Not used or not compliant | Intermittent use of stockings | Full compliance: stockings + elevation |

GS: Greater saphenous; LS: Lesser saphenous.

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Figure 4 Incidence of the post-thrombotic syndrome according to the CEAP classification in patients with deep vein thrombosis during long-term follow-up.[30]
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 [20-22].

Three classifications for PTS have been used by dermatologists and phlebologists 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) [22]. 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 [21]. 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 [18,21]. 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) [23]. 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
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

**Figure 5 Rotterdam approach to the post-thrombotic syndrome according to Wentel et al**

PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

**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.

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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.

**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 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.

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.
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.

Palaroti et al[30] 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[26-23]. 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 reduce 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[31] 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 study 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 µg/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)[24,35].

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REFERENCES

1. Freyburger G, Trillaud H, Labrouche S, Gauthier P, Javorschi S, Bernard P, Grenier N. D-dimer strategy in thrombosis exclusion - a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. *Thromb Haemost* 1998; 79: 32-37 [PMID: 9459318]

2. van der Graaf F, van den Borne H, van der Kolk M, de Wild PJ, Janssen GW, van Uum SH. Exclusion of deep venous thrombosis with D-dimer testing – comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thromb Haemost* 2000; 83: 391-398 [PMID: 10739371]

3. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Sloosman D, Dider D, Unger PF, Patenaud JV, Boumaeaux H. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; 353: 190-195 [DOI: 10.1016/S0140-6736(98)05248-9]

4. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost* 2005; 94: 200-205 [PMID: 16113804]

5. Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. *Ann Intern Med* 2005; 143: 100-107 [PMID: 16027451 DOI: 10.7326/0003-4819-143-2-200507190-00008]

6. Schutgens RE, Ackermark P, Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pigman AH, Prijm MJ, Oltnams R, Kelder JC, Bietsma DH. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation* 2003; 107: 593-597 [PMID: 12566372 DOI: 10.1161/01.CIR.0000045670.12988.1E]

7. Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, Massicotte MP, Hirsh J, Weitz JI, Kearon C. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 1995; 91: 2184-2187 [PMID: 7697847 DOI: 10.1161/01.CIR.91.8.2184]

8. Michiels JJ, Gadisseur A, Van der Planken M, Schryogens W, De Maeseneer M, Hermens JT, Trienekens PH, Hoogsteden H, Pattynama PM. A critical appraisal of non-invasive diagnosis and exclusion of deep vein thrombosis and pulmonary embolism in outpatients with suspected deep vein thrombosis or pulmonary embolism: how many tests do we need? *Int Angiol* 2005; 24: 27-39 [PMID: 15976996]

9. Michiels JJ, Gadisseur A, van der Planken M, Schryogens W, De Maeseneer M, Hermens JT, Trienekens PH, Hoogsteden H, Pattynama PM. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. *Semin Thromb Hemost* 2006; 32: 678-693 [PMID: 17024595 DOI: 10.1055/s-2006-91296]

10. Oudega R, Toll DB, Bulten RJ, Hoes AW, Moons KG. Different
cut-off values for two D­imer assays to exclude deep venous thrombosis in primary care. Thromb Haemost 2006; 95: 744-746 [PMID: 16608150]

11 Kraaijenhagen RA, Piovella F, Bernardi E, Verlato F, Beckers EA, Koopman MM, Barone M, Camporese G, Potter Van Loon BJ, Prins MH, Prandoni P, Bürller HR. Simplification of the diagnostic management of suspected deep vein thrombosis. Arch Intern Med 2002; 162: 907-911 [PMID: 11966342 DOI: 10.1001/archinte.162.8.907]

12 Tick LW, Ton E, Voortuinen TH, Hovens MMC, Leeuwenburgh I, Lobatto S, Stijnen PJ, van der Heul C, Huisman PM, Kramer MH, Huisman MV. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography and D­imer test. Am J Med 2002; 113: 630-635 [DOI: 10.1016/S0002-9343(02)01347-5]

13 Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D­imer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 349: 1227-1235 [PMID: 14507948 DOI: 10.1056/NEJMoa023153]

14 Kearon C, Ginsberg JS, Doukletsis J, Crowther MA, Turpie AG, Bates SM, Lee A, Brill-Edwards P, Finch T, Gent M. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D­imer testing compared with repeated ultrasonography. Ann Intern Med 2005; 142: 490-496 [PMID: 15890460 DOI: 10.7326/0003­4819­142­7­20050405­00007]

15 Meissner MH, Manzo RA, Bergelini RO, Markel A, Strandness DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. J Vasc Surg 1993; 18: 596-605; discussion 606-608 [PMID: 8411467 DOI: 10.1016/0741-5214(93)90069-X]

16 Markel A, Manzo RA, Bergelini RO, Strandness DE. Valvular reflex after deep vein thrombosis: incidence and time of occurrence. J Vasc Surg 1992; 15: 377-382; discussion 383-384 [PMID: 1735898 DOI: 10.1067/mva.2005-08-200025-9]

17 Markel A. Origin and natural history of deep vein thrombosis of the legs. Semin Vasc Med 2005; 5: 65-74 [PMID: 15968582 DOI: 10.1055/s-2005-871743]

18 Siragusa S, Malato A, Anastasio R, Cigna V, Milio G, Amato C, Bellisi M, Attanzio MT, Cormaci O, Pellegrino M, Dolce A, Casuccio A, Bajardi G, Mariani G. Residual vein thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002; 137: 955-960 [PMID: 12484710 DOI: 10.7326/0003­4819­137­12­200212 170-0008]

19 Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D­imer performed after oral anticoagulation is stopped. Thromb Haemost 2002; 87: 7-12 [PMID: 11848459]

20 Palareti G, Legnani C, Cosmi B, Viallonzucchi C, Hirsch M, Quenlenberger P, Schneider B, Welttemann A, Wagner O, Kyrle PA. D­imer levels and risk of recurrent venous thromboembolism. JAMA 2003; 290: 1071-1074 [PMID: 12941680 DOI: 10.1001/jama.290.8.1071]

21 Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzo A, Pattacini C, Testa S, Lensing AW, Tripodi A. D­imer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006; 355: 1780-1789 [PMID: 17065639 DOI: 10.1056/NEJMoa054444]

22 Brandjes DP, Bürller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759-762 [PMID: 9074574 DOI: 10.1016/S0140-6736(96)2215-7]

23 Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, Tornemi D, Mosena L, Pagnan A, Girolami A. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004; 141: 249-256 [PMID: 15313740 DOI: 10.7326/0003­4819­141­4­20040817­00004]

24 Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Głowicki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC, Wakefield TW. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004; 40: 1248-1252 [PMID: 15622385 DOI: 10.1016/j.jvs.2004.09.027]

25 Widmer LK, Plech S, Leu HJ, Boner H. [Venous diseases in 1800 employees. Basel Studies II]. Schweiz Med Wochenschr 1967; 97: 107-110 [PMID: 6032299]

26 Rutherford RD, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: An adjunct to venous outcome assessment. J Vasc Surg 2006; 33: 1307-1312 [PMID: 16082165 DOI: 10.1016/j.jvs.2005.10.07094]

27 Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125: 1-7 [PMID: 8644983 DOI: 10.7326/0003­4819­125­1-1 99607010­00001]

28 Bernardi E, Bagatella P, Frulla M, Simioni P, Prandoni P. Post-thrombotic syndrome: incidence, prevention, and management. Semin Vasc Med 2001; 1: 71-80 [PMID: 15199516 DOI: 10.1055/s-2001-14543]

29 Pesavento R, Bernardi E, Concolato A, Dalla Valle F, Pagnan A, Prandoni P. Postthrombotic syndrome. Semin Thromb Hemost 2006; 32: 744-751 [PMID: 17024603 DOI: 10.1055/s-2006-951460]

30 Roumen-Klappe EM, den Heijer M, Janssen MC, van der Vleeten C, Thien T, Wollersheim H. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. Thromb Haemost 2005; 94: 825-830 [PMID: 16270638]

31 Wentel TD, Neumann HA. Management of the postthrombotic syndrome: the Rotterdam approach. Semin Thromb Hemost 2006; 32: 814-821 [PMID: 17171595 DOI: 10.1055/s-2006-955469]

32 Michiels JJ, Moorsdorp W, Maasland H, Michiels JM, Loo M, Neumann HA, Dulicek P, Svrinova V, Barth J, Palareti G. Duplex ultrasound, clinical score, thrombotic risk, and D­imer testing for evidence based diagnosis and management of deep vein thrombosis and alternative diagnoses in the primary care setting and outpatient ward. Int Angiol 2014; 33: 1-19 [PMID: 24452081]

33 Latella J, Desmarais S, Miron MJ, Roussin A, Joyal F, Kassis J, Solymoss S, Desjardins L, Ginsberg JS, Kahn SR. Relation between D-dimer level, venous valvular reflux and the development of post-thrombotic syndrome after deep vein thrombosis. J Thromb Haemost 2010; 8: 2169-2175 [PMID: 20670369 DOI: 10.1111/j.1538-7836.2010.04001.x]

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