Review

Post-thrombotic syndrome – a position paper from European Society of Vascular Medicine

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Summary: Post-thrombotic syndrome (PTS) is a chronic venous insufficiency manifestation following an episode of deep-vein thrombosis (DVT). It is an important and frequent long-term adverse event of proximal DVT affecting 20–50% of patients. This position paper integrates data guiding clinicians in deciding PTS diagnosis, treatment and follow-up.

Keywords: Thrombosis, deep vein thrombosis, Villalta score, anticoagulant, ultrasound

Epidemiology

Post-thrombotic syndrome (PTS) refers to chronic manifestations of venous insufficiency (CVI) following an episode of deep-vein thrombosis (DVT), being an important and frequent long-term adverse event of proximal DVT within two years in 20–50% of patients. About 5% to 10% of patients develop severe PTS, which may include venous ulcers. Noteworthy, its prevalence has varied widely from one study to another [1]. PTS represents also the most important determinant of reduced quality of life (QoL), similar to that of patients with cancer, angina or heart failure [1].

Different clinical scales have been used to assess PTS. The International Society on Thrombosis and Hemostasis recommends the use of the Villalta scale to diagnose PTS [2]. An important limitation in evaluating PTS prevalence with Villalta scale, is the inability to differentiate PTS from other causes of CVI. Indeed, in almost half of cases signs and symptoms of PTS could reflect a preexisting CVI. Also, the time interval between DVT and PTS assessment impacts the evaluation of PTS prevalence, as well as its severity [2, 3, 4].

Current trend and future projections indicate that the number of adults in the western countries with DVT will double in 2050; therefore, improved prevention and treatment of DVT are critical in decreasing the incidence of PTS. The rate of PTS has recently been found to be much lower in patients with proximal DVT treated with direct oral anticoagulants (DOACs) as compared to that observed in a large cohort of consecutive patients treated with heparin and a vitamin K Antagonist (VKA) [4].

Economic and morbidity impact

Patients with PTS often suffer from pain, cramps, swelling and itching, and, with increasing severity, skin ulcers. These symptoms usually worsen when standing and walking, thereby impacting the QoL of these patients and limiting their daily activities [5]. Several studies have confirmed the negative impact of PTS on patient QoL using either generic (e.g., SF-36) or disease-specific (e.g., VEINES-QOL/Sym) QoL measures. The QoL was worse in patients with more severe PTS [5]. Although estimates of the healthcare costs of treating PTS vary among different studies, it is widely acknowledged that PTS impacts greatly the cost of treating DVT and its sequelae. Indeed, while the health care cost of DVT alone has been estimated at approximately 6,000 USD, the development of PTS complications increases this cost by an additional 75–80%. Venous ulcers are the most expensive complications of PTS. The average cost of treating a venous ulcer was estimated to be 7,900–10,000 USD per patient/year [6]. This cost increase was largely attributable to greater use of healthcare visits and prescription/medications. The high cost of treating venous ulcers is due largely to surgery,

lost workdays and loss of employment. The indirect costs of PTS are also significant: patients with venous ulcers, particularly younger individuals, are absent more often from work, have more job losses, and carry the risk of adverse financial consequences [1].

Pathophysiology

The primary function of the venous circulation is to return blood to the heart. The physiological effects of gravity and hydrostatic pressure hinders the venous return in the upright position. However, a system of valves, an efficient peripheral pump mechanism, and a small dynamic pressure gradient overcome the forces of gravity. The valves function divides the hydrostatic column of blood into segments and prevents retrograde venous flow.

In the veins, thrombus is most often initiated in the sinus of the venous valves, corresponding to the space between the valve leaflet and the adjacent vessel wall [7]. The endothelial thrombotic phenotype is modulated by the local hemodynamic conditions around the valves. In human saphenous veins, the valvular sinus endothelial cells exhibit a more thromboresistant phenotype than the lumen cells [8]. In the sinus, blood circulation is slow with a physiological oscillatory flow pattern. The anti-thrombotic phenotype (low levels of the prothrombotic proteins von Willebrand factor, P-selectin, and intercellular adhesion molecule (ICAM)-1 and high levels of the antithrombotic proteins thrombomodulin, endothelial protein C receptor, and tissue factor pathway inhibitor) disappears when the perivalvular endothelium is exposed to the usual venous blood flow conditions in mice and in human veins at the site of thrombosis, as does the shear-stress induced activation of the transcriptional factors *FOXC2* or *PROX1* [9]. Whether it plays also a role in the resolution of thrombus is unknown.

Following DVT, around 50 to 80% of the vein will be recanalized over months. The biological and cellular mechanisms involved in the thrombus resolution are complex, and none of them alone are predictive of PTS [10]. Rapid resolution of the thrombus, either natural or through therapeutic thrombolysis is associated with a higher likelyhood of valve competence [11, 12]. In some cases, the lysis of the thrombus is not complete. Residual thrombus is replaced by fibrous tissue or cribriform synechiae formed by endothelialized strands of the residual thrombus. Valve leaflets become entrapped, collaterals develop, and the fibrotic process, which may extend to the outer part of the vein wall acts as a functional obstruction and leads to reflux. Both outflow obstruction and reflux together with impaired compliance of fibrotic vein walls eventually induce an ambulatory venous hypertension, defined as a failure to reduce venous pressure with exercise. If the deep vein valves are incompetent, blood simply oscillates within the deep veins, and there is no reduction in pressure. Deep venous obstruction is similarly associated with little reduction in resting pressure, which is dramatically elevated during calf contraction. Long-term sustained venous pressure elevation results in the pathological dilatation of the capillaries, increased endothelial permeability for plasma proteins and erythrocytes in the skin and subcutaneous tissues resulting in oedema, pigmentation, fibrosis and ulceration.

Deep vein thrombosis of the iliocaval or femoroiliac venous segments has a significantly higher risk for PTS than DVT of popliteal-crural veins, as thrombus resolution occurs more slowly and is less complete in the proximal venous segments. Patients with both chronic obstruction and reflux have the highest incidence of severe PTS with skin changes and ulceration [13].

Risk factors

Optimal knowledge of clinical, biologic and ultrasonographic risk factors for PTS is crucial to better identify DVT populations at risk for PTS, and to identify therapeutic targets. The risk factors of PTS have been grouped according to time points of follow-up after acute DVT: risk factors apparent at the time of DVT diagnosis, and risk factors apparent during follow-up. As far as the former are concerned, the following independent risk factors for PTS have been identified: the proximal location of DVT (especially when involving the iliac or common femoral segments), which increases the risk by 2–3 times; preexisting venous insufficiency, which increases the risk up to twofold; obesity (BMI > 30 kg/m^2), which more than doubles the risk of PTS; older age, which increases the risk threefold; and the severity of symptoms at the onset of DVT [14, 15]. Conversely, the following factors appear to have no or little effect on the risk of developing PTS: sex, the nature of DVT (provoked or unprovoked), and inherited thrombophilia.

As far as risk factors appearing at follow-up are concerned, the following have been identified: persistent symptoms and signs one month after the acute DVT episode, residual venous obstruction on compression ultrasonography and popliteal valvular reflux evaluated 3–6 months after DVT diagnosis. Some inflammation markers, such as C-reactive protein (CRP); interleukin-6 (IL-6), IL-8, IL-10, and ICAM-1, higher levels of matrix metalloproteinase (MMP)-1 and MMP-8, measured at varying time points after DVT diagnosis have been found to be associated with a higher risk of PTS. Also, subtherapeutic anticoagulation with VKAs during the first 3 months of DVT treatment increases the risk of PTS approximately twofold [4, 14]. Noteworthy, the most important risk factor is ipsilateral recurrent DVT, which increases the risk of PTS by 6–8 times. Accordingly, prevention of recurrent thrombotic events is the cornerstone of PTS prevention.

Clinical and instrumental diagnosis

Clinical scale and scores

The ideal scoring system for PTS diagnosis should be easy to use, validated, specific, have a good interobserver reliability, be acceptable to patients, have a clear

association with the pathophysiologic mechanisms, and reliable enough to categorize the disease severity and to identify its improvement or deterioration over time. Several scoring systems or classifications for grading the severity of PTS have been proposed, including the Villalta scale [16], Ginsberg measure [17] and Brandjes score [18]. Although Widmer and Clinical-Etiological-Anatomical-Pathophysiological (CEAP) [19] classifications and the Venous Clinical Severity Score (VCSS) have been originally developed for patients with CVI, they can occasionally be applied to the grading of PTS.

The Villalta scale assesses five symptoms (pain, cramps, heaviness, paresthesia, pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression). Each variable has a 4-point scale ranging from 0 (absent) to 3 (severe). PTS is diagnosed if the Villalta score is ≥ 5 or if a venous ulcer is present. A score of 5–9 is categorized as mild, 10–14 as moderate, and ≥ 15 as severe. The Villalta scale, combined with a venous disease-specific quality of life questionnaire, is the most suitable tool for the diagnosis and classification of PTS [20]. The Ginsberg measure was designed on the basis of persistence of symptoms or development of new symptoms six months after an initial DVT. The criteria are: a) persistent swelling and leg pain for one month after DVT; b) pain and swelling developing at least six months after DVT; c) relief from these complaints by rest and leg elevation. In comparison to the Villalta scale, the Ginsberg measure is more likely to identify the most severe disease findings.

The Brandjes score is composed of a list of objective symptoms and subjective signs, which in turn are graded as absent or present. A diagnosis of mild-moderate PTS is made if the score is 3 or higher (including one objective criterion), whereas a diagnosis of severe PTS is established if the score is 4 or more [18].

The Widmer classification grades patients into classes I, II and III [19].

The CEAP classification categorizes the CVD according to clinical signs (C), aetiology (E), anatomic distribution (A), and pathophysiology (P).

The VCSS gives additional weight to the most severe manifestations of CVD (CEAP clinical class 4–6). The Villalta scale appears to be the most commonly used due to its ease and versatility of use in diagnosis and categorization of severity. Indeed, in 2008 the International Society on Thrombosis and Haemostasis recommended the Villalta scoring system to be utilized in clinical trials as the scoring system of choice for the diagnosis and grading of PTS [20, 21].

Ultrasonography

The available diagnostic tools used in patients with PTS are the physical examination and additional tests, including continuous wave [CW] Doppler, duplex ultrasound [DUS], phlebography, plethysmography, venous pressure measurement, and modern imaging techniques such as magnetic resonance venography [MRV] and computed tomography venography [CTV]. The European Society for Vascular Surgery (ESVS) guidelines recommend DUS for routine use; non-invasive Doppler and plethysmography (except certain parameters of air-plethysmography) have lost most of their value, and are no longer used in the routine evaluation of CVD; the ESVS Guidelines recommend against CW Doppler use in CVD [22].

CTV and MRV have evolved significantly in recent years, so that it is now possible to obtain detailed three-dimensional reconstructions of the venous system. Ilio-caval and pelvic venous pathology (post-thrombotic obstruction, venous compression/stenosis like Nutcracker syndrome or May-Thurner syndrome and pelvic varicocele) can be reliably identified. However, given the heterogeneity of the published studies, there is insufficient scientific evidence to adequately judge the true effectiveness of the two techniques for visualization of the venous vasculature.

Ultrasonography plays a key role in the identification of patients at risk of PTS development. In a systematic review and meta-analysis study, data bases were searched for prospective studies including consecutive patients with DVT who had received standardized treatment [23]. The patients had an ultrasound evaluation during follow-up aimed at assessing findings consistent with vascular damage after DVT. They had a follow-up period of at least 6 months for the occurrence of PTS, as assessed by a standardized protocol. Two parameters were found to predict PTS: residual vein thrombosis and venous reflux, defined according to standardized methods and criteria [24]. Residual vein thrombosis is defined as the presence of thrombotic material after compressibility of at least 4 mm in the transverse section [25]. The presence of a retrograde flow through the popliteal valve after a standardized compression of the mid-thigh, persisting after repeating the manoeuvre with a tourniquet to prevent the influence of superficial vein reflux, is considered suggestive of valve incompetence [4]. An incompetent vein is defined by an abnormal valve closure time that produces a greater than 0.5 seconds reversal flow [24].

In a study involving 120 lower extremities of 105 patients who had a first episode of DVT, Labropoulos et al. reported that limbs with both reflux and obstruction were more likely to develop skin damage than those with reflux or obstruction alone. Comerota et al. investigated the relationship between residual thrombus and symptoms of PTS, and found a direct and significant correlation of CEAP and Villalta scale with residual thrombus, suggesting that residual thrombus is associated with an increased risk of PTS [24, 25].

Is it possible to prevent the PTS?

Catheter-directed pharmaco/mechanic thrombolysis

The earlier recanalization of obstructed vessels with the use of thrombolytic drugs has long been advocated in order to decrease the rate of PTS. In recent years, because of the

high hemorrhagic risk associated with the intravenous infusion of streptokinase or urokinase the use of catheter-directed thrombolysis (CDT), alone or associated with mechanical procedures (thrombus fragmentation, iliac veins angioplasty followed by stenting as appropriate) has gained increasing popularity. Whether, however, it is associated with a favorable benefit/risk profile is still uncertain.

So far, the results of three randomized controlled clinical trials addressing the value of CDT for prevention of PTS, as defined according to the Villalta scale, have been published. In the CaVenT study, 209 patients with ilio-femoral DVT were randomized to receive anticoagulants alone or preceded by CDT (alteplase) [26]. After two years of follow-up, there was a borderline significant reduction (15%) in PTS development in patients treated with additional CDT. The reduction was even stronger after five years of follow-up [27]. However, severe or clinically relevant bleeding complications developed in 8% of patients allocated to CDT and in none of those receiving heparin alone [26], and no appreciable improvement in patients quality of life was recorded [27]. In the ATTRACT study, 691 patients with proximal DVT were allocated to pharmaco/mechanic CDT followed by anticoagulation or anticoagulation alone [28]. Although there was no difference in the PTS development, as assessed with the Villalta scale after 6 and 24 months, between the two study groups, the incidence of moderate/severe PTS was found to be significantly reduced in the subgroup of patients with iliofemoral thrombosis treated by endovascular approach [29]. However, the incidence of major bleeding was significantly higher in the group of patients allocated to the CDT [28]. Finally, in the CAVA study 152 patients with iliofemoral DVT were randomized to receive ultrasound-assisted pharmaco/mechanic CDT (urokinase) followed by anticoagulation or anticoagulation alone [30]. After one year of follow-up, there was a slight trend favoring CDT over anticoagulation alone in terms of PTS development (29% vs 35%), but the small advantage was offset by a higher risk of major bleeding (4 events vs 0), and no appreciable difference in patients quality of life was observed between the two groups [30].

In conclusion, because of its invasiveness, the associated risk of major bleedings and the uncertainty about its efficacy, at present CDT cannot be recommended in patients with proximal DVT. An exception can be made for young people with a threatening clinical presentation imputable to a recent iliofemoral DVT provided the bleeding risk is low and there are considerable expertise and resources.

Recently, a systematic review and meta-analysis demonstrated that in patients with iliofemoral DVT percutaneous mechanical thrombectomy was associated with a higher cumulative 6-month primary patency and a lower incidence of major bleeding compared to thrombolysis. However, considerable heterogeneity within groups did not allow for between-group comparison of PTS [31].

Elastic compression stockings

Elastic compression stockings (ECS), by reducing edema and counteracting venous hypertension generated by residual vein thrombosis and venous reflux, could plausibly play a role in preventing PTS. In two small randomized studies, published 15–20 years ago, the use of below-knee ECS (30–40 mm Hg at the ankle) for at least two years was found to reduce by approximately 50% the incidence of both overall and severe PTS [32, 33]. Subsequently, below-knee ECS were found to be as effective as full-length stockings while increasing patients compliance and tolerability [34]. By contrast, a recent large, double-blind randomized clinical trial (the SOX study) failed to confirm the advantage of ECS [35]. Indeed, after two years of follow-up the incidence of PTS was found to be 14.2% in the 410 patients randomized to wear active below-knee ECS, and 12.7% in the 396 allocated to the placebo ones ($p = 0.58$). However, due to the unexpectedly low compliance (overall, lower than 50% of recruited patients), the conclusions of this study have generally been criticized. Of interest, following the publication of the OCTAVIA study, which failed to show the non-inferiority of a 1-year over a 2-year course of ECS for PTS prevention [36], a recent meta-analysis of available controlled studies turned out to indicate a trend favoring the use of ECS (OR 0.56; 95% CI 0.27–1.16) [37]. Recently, the IDEAL DVT trial, a multicenter, randomized trial compared the effectiveness of individualized duration of ECS with standard duration (24 months) of ECS for the prevention of PTS in 856 patients with proximal DVT. All had received below-knee ECS for six months, and the trial concluded that shortened six months ECS therapy was non-inferior to two years of therapy [38]. This strategy proved to be highly efficient, as treatment could be stopped in 55% of patients at six months, and in an additional 11% of patients at 12 months.

In summary, apart one negative trial, all current evidence suggests a beneficial effect of ECS to prevent PTS in patients after DVT. We conclude that an individualized therapy plan with ECS can shorten the duration of therapy, and in such a way increases patients' compliance and reduces health-care costs while preserving efficacy.

Initial DVT treatment with DOACs

The persistence of residual vein thrombosis (RVT) [39] and the inadequacy of VKA treatment [40] are likely to play a key role in the development of PTS. Unfortunately, the use of conventional VKA treatment results in the persistence of thrombotic burden, as detected by compression ultrasonography three months after the acute episode, in approximately 50% of patients [41]. In addition, the time spent in the therapeutic range while on VKA treatment rarely exceeds 50% even in the hands of experienced physicians and in the context of well-conducted clinical trials.

The novel directs oral anticoagulants (DOACs) have now become commercially available worldwide. They have

consistently been found to be at least as effective as and safer than VKAs for the treatment of patients with acute venous thromboembolism (VTE) [42]. Because of their predictable pharmacokinetics, they can be used in fixed dose, without laboratory monitoring, and result in a much more stable anticoagulation than that induced by VKAs. Their use for the initial treatment of DVT is associated with a lower incidence of residual vein thrombosis than in patients treated with VKAs [43], and is likely to reduce the incidence of PTS. Recently, with the adoption of the Villalta scale the rate of PTS was assessed in a consecutive series of 309 outpatients with acute proximal DVT who had received at least three months of treatment with a DOAC and had been followed-up for up to three years [4]. The rate of PTS development was compared with that recorded in a historical cohort of 1036 consecutive patients who had been treated with VKAs and had received a similar follow-up examination. At the end of the follow-up period, PTS developed in 87 patients (28.2%) treated with the DOACs (severe in 12), and in 443 patients (42.8%) treated with VKAs (severe in 61). After adjusting for baseline differences between the two groups, the risk of PTS in the DOAC-treated patients was reduced by 54% in comparison to patients treated with conventional anticoagulation (odds ratio 0.46; 95% CI, 0.33 to 0.63).

These results have recently been confirmed by a systematical review and meta-analysis of all available studies addressing the comparison between rivaroxaban and VKAs for the prevention of the PTS. The extent by which rivaroxaban was found to reduce the incidence of PTS was not only statistically significant, but also clinically relevant, as the most severe manifestations were as likely to be prevented as were the less severe ones [44]. In conclusion, the results of this study suggest that in patients with acute DVT the use of the novel direct anticoagulants has the potential to offer not only a more practical and safer approach but also a more favorable prognosis in terms of PTS development compared to conventional treatment with VKAs.

Is it possible to identify patients with different risk? Can PTS be predicted?

Up to now, two scores have been derived that can help predict the development of PTS at patient presentation with DVT, the former generated from the SOX study [45], the latter from the IDEAL DVT study [46].

The SOX PTS model includes three independent predictors and has a range of possible scores from 0 to 5 [45]. High-risk predictors are: index DVT in the iliac vein; body mass index of $\geq$ 35; and moderate-severe Villalta severity category at DVT diagnosis (Table I). As compared with patients with a score of 0, those with a score of $\geq$ 4 had an odds ratio of 5.9 (95% CI: 2.1–16.6) for developing PTS. This score requires external validation before it can be considered for clinical use.

Table I. SOX PTS score for the prediction of PTS. For a score $\geq$4 the OR of developing PTS is 5.9 (95% CI 2.1–16.6)

Features	Score
Iliac vein involvement	1
BMI >35 kg/m^2	2
Moderate (score 5–9) Villalta score	1
Severe (score $\geq$10) Villalta score	2

Table II. IDEAL PTS score for the prediction of PTS. Baseline model: 0–2 points: 10%; 3–4 points: 20%; $\geq$5 points: 40%. After six months: 0–2 points: 25%; 3–4 points: 45%; $\geq$5 points: 60%

Features	Baseline risk assessment	Risk assessment after 6 months
Age >56	2	1
Body mass index >30 kg/m^2	2	1
Varicose veins	4	3
Smoking	1	1
Residual thrombosis	–	1
Female gender	1	–
Provoked deep vein thrombosis	1	–
Iliofemoral deep vein thrombosis	1	–
History of deep vein thrombosis	1	–

The IDEAL PTS model includes a higher number of variables [46], and can be calculated at baseline and after six months (Table II). It was derived in a Dutch cohort and validated in an Italian cohort. Optimism-corrected area under the receiver operating characteristic curves (AUCs) were 0.71 for the baseline model and 0.60 for the secondary model. Calibration plots showed well-calibrated predictions. External validation of the derived clinical risk scores was successful: AUC, 0.66 (95% CI: 0.63–0.70) and 0.64 (95% CI: 0.60–0.69).

However, at present, the value of these scores is uncertain, as is their potential implications for clinical practice. It is too early to recommend them for the systematic prediction of PTS in patients with DVT [47].

Treatment of PTS

When PTS has developed, we should try to treat it to reduce symptoms, deterioration in quality of life and patient disability. A standard and effective management for PTS treatment is lacking. Treatment of PTS is primarily based on ECS, exercise and lifestyle modifications. The effectiveness of various pharmacologic agents for PTS treatment remains controversial. Surgical or radiological interventions for vein reconstruction or revascularization may be considered in refractory cases.

Based on recent data, the management of patients should be tailored to individual situation and needs [38, 48].

Table III. Main lifestyle changes and self-care in patients with PTS

Walk frequently	Avoid constrictive clothing
Rest with legs elevated during pauses whenever possible	Wear comfortable shoes, avoid high heels
Raise the feet of the bed (10–15 cm) if no contraindication	Avoid sunbathing for too long
Maintain moistened skin to prevent drying or cracking	Avoid sauna, thermal baths
Take cold showers	

Life style, exercise, manual lymphatic drainage

In patients with PTS, pharmacological and non-surgical interventions aim at preventing venous disease progression and complications, reduction of symptoms, and improvement of quality of life. Excepting ECS, physical therapies are seldom or partially mentioned in guidelines. Lifestyle adaptations may be advised in patients with PTS aiming at improving quality of life by reducing venous stasis and related symptoms (Table III). Physical exercise may be useful to increase efficacy of mechanisms facilitating venous return. Exercise has been shown to enhance microvascular endothelial function, thus increasing venous flow [49–51]. Walking exercise should be encouraged to enhance calf muscular contractions and plantar loading as well as joint flexibility to enhance venous drainage [52–55].

Exercise not only facilitates venous returns, but also plays a role in preventing or slowing down PTS development. Indeed, walking exercise implemented early after DVT diagnosis, associated with early compression, not only reduce DVT-related symptoms [1, 56, 57], but leads to reduce residual vein occlusion, and consequently reduce PTS development [58]. Venous hypertension, a hallmark of PTS, may be associated in the long run with lymphatic overload. Based on this hypothesis, therapies decreasing lymphatic overload may improve PTS symptoms. A small trial showed that complex lymphatic treatment, including ECS and manual lymphatic drainage in patients with PTS was safe, well-tolerated and effective [59]. Even if few of these advices are supported by evidences, which they should be considered in the global management of PTS patients.

Elastic compression

In contrast to the uncertainty surrounding the use of ECS for PTS prevention, they play a role in PTS treatment, although their use is based primarily on extrapolation from patients with primary CVI, the low risk of harm and the possibility of benefit for at least some PTS patients. ECS have been reported to reduce symptoms of CVI and PTS such as limb swelling and contribute to functional improvement. An initial therapeutic trial of 20 to 30 mmHg knee-length ECS can be followed by stronger pressure stockings (30–40 or 40–50 mmHg) if lower pressure stockings are ineffective [1, 14]. For patients with severe symptoms unresponsive to ECS, venous-return assist device (Venowave) is recommended, and intermittent pneumatic compression can also be a valid therapeutic option for patients with moderate to severe symptoms [14]. Caution in the use of elastic compression should be taken in patients with severe peripheral artery disease, and a threshold below which no compression is advised has been advocated for patients with a blood pressure, as measured at ankle, lower than 50 mmHg. This threshold may not be appropriate for diabetic patients, in whom toe pressure measurement could be more useful [60].

The role of continuing anticoagulation

Although it is common clinical practice to prolong anticoagulation in patients with severe PTS, it is uncertain whether having PTS increases the risk of ipsilateral recurrent VTE after stopping anticoagulation. Providing anticoagulation of appropriate duration for treatment of the initial DVT is recommended as a mean of reducing the risk of recurrent DVT and consequent PTS. There is no consensus on the value of extending anticoagulation in patients with established PTS beyond the duration recommended for the treatment of DVT [1].

Venoactive medications

Venoactive drugs that have been considered for the treatment of PTS include rutosides (thought to reduce capillary filtration and microvascular permeability), defibrotide (downregulates plasminogen activator inhibitor-1 release and upregulates prostacyclin, prostaglandin E2, and thrombomodulin), and hidrosmin (mechanism of action unknown). Currently, there is limited and low or very low quality evidence that venoactive medications reduce the symptoms of PTS [61]. Furthermore, there is no evidence that diuretics are effective for the treatment of PTS-related edema.

Endovascular and surgical treatment of post-thrombotic syndrome

Despite optimal anticoagulation therapy of patients with proximal DVT, there is still a high number of patients suffering from PTS due to chronic venous obstruction, suboptimal collateralization, and deep vein valvular dysfunction. In the last two decades endovascular catheter-based treatment modalities have been tested and used for the

treatment of acute extensive DVT as well as of post-thrombotic changes in the cava and iliac veins in an attempt to reduce the incidence and severity of PTS symptoms in selected patients [1, 62].

Early studies suggested that catheter-based endovascular therapy can be applied in symptomatic patients with chronic iliocaval obstruction, resulting in reduction of PTS severity.

Recently, Garcia et al. showed that percutaneous transluminal venoplasty in combination with ultrasound-accelerated thrombolysis can result in successful recanalization of chronic venous obstruction with improved PTS severity and quality of life [63].

PTS can lead to severe chronic venous insufficiency, which is often the result of both deep vein obstruction and reflux. Obstruction typically involves the iliocaval and common femoral vein segments, while deep vein reflux, caused by valve damage, concerns the femoropopliteal segment.

In patients with advanced PTS, in addition to standard therapies and with the intent to obtain symptoms relief, proximal obstruction can be treated by catheter-based endovascular technique [64]. In case of concomitant valvular incompetence, obstruction treatment should be the first therapeutic step, while surgery for deep reflux correction should be undertaken only if symptoms persist or worsen over time [65].

Despite the weak quality of evidence, the percutaneous venoplasty and stenting may be considered as a beneficial and safe treatment option in patients with severe obstructive venous disease to limit progression to PTS [66, 67].

The results of deep reflux correction surgery are difficult to assess, as series are small and different techniques are described. In PTS valve surgery, a meta-analysis of the available techniques (transposition, transplant, neovalve construction) after more than five years showed successful outcomes ranging from 50 to 75% with a low rate of complications [68].

In conclusion, operative treatments for PTS, both endovascular and open surgery, should today be considered as possible therapeutic options for patients affected by disabling CVI with the purpose of improving the quality of life and preventing ulcer recurrence. These interventions should be performed in a high-skilled multidisciplinary centre, in which the vascular physician/angiologist, often the doctor who take care of these patients, shares the clinical evaluation with the technical aspects together with vascular surgeon and endovascular specialist (interventional angiologist/interventional radiologist).

The American Venous Forum Guidelines state that in a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis with or without lower extremity deep reflux disease that is associated with CVI C3–C6, angioplasty and stent recanalization are recommended in addition to standard compression therapy [69].

Surgical treatment of post-thrombotic valvular incompetence is suggested in patients with infrainguinal deep venous reflux and skin changes at risk of venous ulcers (C4b) or healed/active ulcer (C5–C6), in addition to standard compression therapy [69].

Conclusions

Treatment of PTS is primarily based on ECS, exercise and lifestyle modifications. The effectiveness of various pharmacologic agents for PTS treatment remains controversial. Surgical or endovascular interventions for valve reconstruction and/or recanalization can be considered in disabling cases.

PTS remains a serious, disabling condition, still with many diagnostic, clinical and therapeutic aspects that must be addressed with future studies [70]. Scientific societies must promote attention to this disease and share clinical experiences in order to standardize management and improve the quality of care.

Based on the evidence reviewed above, the position of the European Society of Vascular Medicine is as follows:

- Post thrombotic syndrome is an important cause of patient ill health and provides a significant cost to the health service and patient.
- Clinical scales may be useful to predict the development of PTS.
- Anticoagulation with DOACs rather than VKAs may reduce the development of PTS.
- Compression stockings are likely to reduce the development of PTS and should be used for at least six months following DVT.

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History
Submitted: 06.02.2021
Accepted: 15.02.2021
Published online: 15.03.2021

Conflicts of interests
No conflicts of interest exist.

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