

# Post-thrombotic syndrome prevention – do we really know the predictive factors?

## Prävention des Postthrombotischen Syndroms – kennen wir wirklich die prädiktiven Faktoren?

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### ABSTRACT

Despite an increasing knowledge and experience regarding deep vein thrombosis (DVT) treatment, the rate of post-thrombotic syndrome (PTS) remains still relatively high. According

to the current knowledge it is still difficult to predict on the individual basis, who of the DVT patients will develop PTS as late complication of the vein thrombosis. Among the factors influencing the higher prevalence of PTS, the ipsilateral DVT recurrence is of the highest importance. The other factors which should be mentioned are age, obesity, previous chronic venous disease as well as a proximal DVT location or lack of symptoms' resolution in the early treatment. Looking for the most effective PTS prevention method several clinical trials were performed regarding pharmacological DVT treatment, use of early mobilization and medical compression stocking as well as an implementation of the thrombectomy and thrombolysis. This paper presents a review of the current knowledge regarding the PTS predictive factors and prevention.

### ZUSAMMENFASSUNG

Obwohl wir zunehmend mehr über die tiefe Beinvenenthrombose (TBVT) wissen und mehr Erfahrung im Umgang damit haben, bleibt die Rate des post-thrombotischen Syndroms (PTS) relativ hoch. Es ist heute noch sehr schwer, nach der Diagnose der tiefen Beinvenen-Thrombose vorherzusagen, welcher Patient ein PTS entwickeln wird. Unter den Faktoren, die eine höhere Prävalenz des PTS bedingen, finden wir als wichtigstes Kriterium das ipsilaterale Thrombose-Rezidiv. Außerdem scheinen Alter, Übergewicht, vorausgegangene chronische venöse Insuffizienz sowie eine proximale TBVT oder die ausbleibende Symptomrückbildung nach Start der Behandlung Risikofaktoren für ein PTS zu sein.

Mit Blick auf eine möglichst effektive PTS-Vorbeugung wurden viele klinische Studien zur Pharmakologie, zur frühen Bewegung und zum Einsatz von medizinischen Kompressionsstrümpfen bis hin zur chirurgischen Thrombektomie und Thrombolyse aufgelegt.

In dem vorliegenden Artikel wird die Datenlage in Bezug auf Vorhersagefaktoren und Prävention des post-thrombotischen Syndroms zusammengetragen.

## Post-thrombotic syndrome prevalence and assessment

Post-thrombotic syndrome (PTS), being the late sequelae of the deep vein thrombosis (DVT) concerns from 10 to 70 % of lower leg DVT patients (1, 2, 3). Among the factors influencing the reported PTS prevalence, both, the potentially predictive factors as well as the way of PTS evaluation and assessment should be mentioned (1, 2, 4). Among the methods used to diagnose PTS as well as to assess the PTS severity, various tools and criteria were used (4).

In the recent years, the majority of the performed studies used the Villalta score based on the venous disease symptom and signs assessment for PTS presence and severity evaluation (4, 5). An implementation of this score for PTS assessment has been recommended by the International Society on Thrombosis and Hemostasis, however, its weakness as well as unspecificity as an objective tool for diagnosing and PTS scoring is recently discussed and criticized (6). In term of the proper planning of further research, current PTS diagnostic criteria should be probably revised. There are other scores, like Ginsberg criteria or Brandjes score, as well as the scores commonly implemented in the chronic venous disease evaluation (such as CEAP, rVCSS), but they neither seem to be sufficient.

## Post-thrombotic syndrome predictive factors

Looking for the PTS predictive model, various groups of the factors should be evaluated, including the factors related to the patient initial status (characteristics of the patient), the factors related to the initial DVT episode, as well as the factors related to the way of the treatment (1, 2, 4).

**DVT recurrence:** One of the major factors influencing on the PTS occurrence is the ipsilateral thrombosis recurrence leading to the 2–10 times higher risk of PTS (2, 3, 4, 7). Knowing this, the proper anticoagulant treatment oriented to reduce the recurrence risk, always considering the risk/benefits ratio of the anticoagulant treatment is crucial (8).

**Anticoagulation:** It is important to respect the minimal duration, at least 3 months' anticoagulation in the patients with temporary risk factor and longer or life-long therapy in unprovoked DVT cases (2, 3, 4) and the sufficient dose, specially in the first 3 months. Duration of the anticoagulation treatment longer than standard by itself seems not to influence the risk of PTS occurrence, provided the proper duration of the anticoagulation is respected. The value of insufficient intensity of anticoagulation in patients on vitamin K antagonists (subtherapeutic INR values) is emphasized, especially during the first 3 months of the therapy (4, 9–13). On the other hand, there is no clinical confirmation that a high intensity of anticoagulation over the therapeutic value results in a lower PTS rate (12, 13).

**Patient:** Among the risk factors related to the patient initial status, the most important are the age of the patient by the time of the thrombosis, obesity as well as previous chronic venous disease presence. The older age of the DVT patient is related to an increased PTS risk (with 30 % to the 3-fold higher PTS rate) (2, 3, 4). The relationship between obesity and chronic venous disease (CVD) symptoms as well as disease progression is well known from studies concerning the primary venous disease. In DVT patients, the presence

of obesity leads to the more than 2-fold increase in PTS rate (2, 3, 4). Another important factor related to higher PTS occurrence is the presence of varicose veins already before the DVT onset (3, 4). Preexisting varicose veins in DVT patients resulted in at least 2-fold increase of PTS rate (4). On the other hand, according to several studies up to 40 % of all diagnosed PTS might be related at least in part to a preexisting chronic venous disease (14). Thrombophilia (3, 4, 15) or gender (2, 3, 4) was not related to higher PTS rate.

**Causes and clinical manifestation of DVT:** PTS can be found in both, symptomatic and asymptomatic DVT courses (1, 3, 4). There is also no significance difference in the PTS prevalence between a provoked and unprovoked DVT etiology (1, 3, 4). In term of the DVT location, the higher prevalence of the PTS is reported in patients with a proximal lower leg DVT. However, the risk of the PTS occurrence is also present in distal, calf vein, DVT cases (1, 3, 4).

**Residual Thrombus:** The presence of the residual DVT symptoms during the treatment course as well as the presence of the residual thrombotic changes in the vein in duplex investigation during the follow up period, seem to be the important factors influencing on the final treatment outcome (1, 3). Residual thrombosis presence after DVT treatment increase the risk of PTS occurrence at least 1.6 times in the patients treated conservatively (1). A recent study by Comerota et al. documented the statistically significant correlation between residual thrombosis after catheter directed thrombolysis treatment and PTS occurrence in the ilio-femoral DVT (16).

Despite the performed research, in the available literature, many questions regarding the PTS predictive factors remain still unanswered. Further research dedicated to the validated PTS predictive model creation should be based on objective PTS criteria and assessment methods.

## Post-thrombotic syndrome predictive models

An increasing knowledge and research dedicated to the potential PTS predictive factors resulted in the PTS predictive model construction. The main goal of this models is the possibility to select the patients at highest risk of PTS occurrence. Their clinical efficacy needs to be proven in further research on larger groups of patients.

In the Canadian VETO study (Venous Thrombosis Outcomes) 359 DVT patients were evaluated (17). Clinical assessment was performed at baseline, and at 1, 4, 8, 12 and 24 months. PTS positive predictive factors were: age, previous DVT episode, atherosclerosis risk factor presence [hypertension, high cholesterol, higher BMI], longer duration of symptoms before DVT diagnosis and work in a job with high physical demands. Among the factors not influencing the PTS occurrence the following were identified: sex, location of DVT (proximal vs. distal), side of DVT (left vs. right), type of DVT (cancer-related, temporary risk factors [e.g. surgery, trauma] or idiopathic), initial anticoagulation with LMWH or UFH, or duration of warfarin therapy.

Van Rij et al prospectively analyzed the clinical outcome of 114 acute DVT patients (18). Within 7–10 days after DVT diagnosis all the patients underwent a further review with clinical examination, ultrasound and air plethysmography with subsequent follow up examinations up to 5 years. The following factors were identi-

fied as the best predictors for PTS occurrence: extensive clot load on presentation; <50 % clot regression at 6 months; venous filling index > 2,5 mL/sec and abnormal outflow rate (<0.6). Patient with three or more of this factors had a significant risk of developing PTS with sensitivity of 100 % and specificity 83 %.

In the post hoc analysis of the SOX trial cohort, the SOX – PTS index was calculated and proposed (19). The high predictors of the PTS occurrence were the following factors from the baseline assessment: iliac vein DVT (1 point), BMI > 35 (2), Villalta score 9–14 at baseline (1), Villalta score > 14 at baseline (1). According to this model, the score  $\geq 4$  is related to almost 6 fold increase of the PTS risk [OR 5.9 (95 % CI 2.1–16.6)].

In the model published in 2018 by Amin et al. not only the baseline risk assessment but also the risk assessment in the subacute phase was proposed (6 months after DVT diagnosis) (20). Concerning the baseline assessment, the age > 56 years (2 points), BMI > 30 (2), varicose veins (4), smoking (1), female sex (1), provoked DVT (1), ilio-femoral DVT (1), positive DVT history were selected as the clinically important. The score 3–4 from the baseline assessment reflected 30 % risk of PTS occurrence; in the patients with 5 point score the clinical probability was at the level of 40 %. In the secondary model (secondary evaluation performed 6 months after DVT onset) among the factors of the greatest importance for PTS occurrence the following were found: age > 56 years (1), BMI > 30 (1), varicose veins presence (3), smoking (1), residual vein obstruction (1). In patients with a secondary assessment score of 3–4 points the PTS risk was 45 % and for the score of 5 points it was 60 %. For now, the models proposed and described above allow to predict the clinical PTS probability only. According to the current research, we are probably still not able to predict (on the individual basis) which of the patient will and which will not develop PTS after a DVT episode. Further research is also needed in this area, especially the research based on the proper objective methodological criteria regarding PTS diagnosis and severity assessment which are still lacking and have to be developed.

## Post-thrombotic syndrome prevention methods

An avoidance of DVT occurrence remains the best way of the PTS occurrence prevention (1). Unfortunately, despite the number of guideline documents dedicated to the various patient populations we still do not know measures which allow to avoid all DVT cases (even, if with the properly implemented antithrombotic prophylaxis protocols, the DVT risk only significantly decreases) (21–24). Among the other important factors related to the still high DVT prevalence are: the growing age of the population, the lack of the proper VTE awareness among the medical staff as well as in the patient populations and also the gap between the guideline recommendation and “real world” clinical practice.

As previously mentioned, in the patients with already present DVT, some PTS predictive factors can be identified, but the final DVT episode outcome remains difficult to predict in term of the PTS occurrence in the single particular patient case. According to the performed research, to lower the risk of PTS occurrence in the post-DVT patients, some clinical attempts have been proposed in-

cluding compression use, anticoagulation treatment modification or an invasive early vein lumen reopening. On the other hand, we do not know if the modification of the other PTS risk factors (such as obesity or previous chronic venous disease) in the disease course can result in the PTS rate reduction.

## Compression stocking in PTS prevention

Compression stocking is one of the important compounds of the DVT patient treatment algorithm, facilitating the patient mobilization as well as lowering the severity of the local complains (including DVT related pain and leg swelling). In the current literature at least six RCTs reported benefits of compression in reducing incidence of PTS (25–30). As found out in the randomized controlled study performed by Prandoni and coworkers, the use of the below knee class II compression stocking in DVT patients within a 2 years period after the DVT episode, reduced the PTS prevalence in the late follow up phase from 49 % in the control to 26 % in the compression group (mean follow up duration 49 months (26).

Brandjes et al randomized 194 patients with proximal symptomatic DVT into two groups: one wearing 30–40 mm Hg knee length compression stockings or to the control group, without stockings. In the follow up period (mean 76 months) 50 % reduction in the PTS occurrence in the stocking group was noticed (25). In the study of Blättler and Partsch the early mobilization of the DVT patients wearing compression stockings resulted in significant reduction of local complains as well as lower postthrombotic syndrome rate in the late follow up phase (31).

Despite the data from several previously published RCTs, after the SOX trial result publication (comparison of the efficacy of the class II below the knee compression stocking with placebo stocking), the role of the compression in the PTS prevention started to be questioned (32). According to the SOX trial results, the comparison of both groups did not result in the statistically significance difference in the PTS rate (assessed by Ginsberg criteria) between the groups (cumulative PTS rate 14.2 %/active ECS/ vs. 12.7 %/placebo ECS/(HR 1.13; 95 % CI 0.73–1.76;  $p = 0.58$ ). Several methodological problems related to the SOX trial were discussed after the study result publication, specially the fact that the start of the use of compression was relatively late in both groups and that the compression stockings were sent by post and nobody introduced the patient to the skills of putting them on the leg. Compliance, as one could expect in consequence, was very low in both groups. On the other hand, on the base of these results in many (after SOX trial era) guideline documents, the use of the compression in PTS prevention was not recommended (ACCP 2016) (1,8).

The Cochrane analysis published in 2017 on the base of 10 RCT analysis suggests (with a low level of evidence) that the patients with DVT who wear elastic compression stockings are less likely to develop PTS RR 0.62 (95 % CI 0.38–1.01), although no significant differences concerning severe PTS occurrence were observed (RR 0.76 (95 % CI 0.53–1.15) (33). The authors of the most recent (2017) guidelines concerning the use of medical compression stocking (MCS) in venous and lymphatic disease downgraded the recommendation for the PTS prevention by MCS in acute DVT. Compression is recommended not only to decrease pain and swelling in DVT, as well as to mobilize the patient, but also to prevent post-thrombotic syndrome occurrence (this last indication recommendation

grading was changed from 1 A in the previous guidelines to 1B in the current document) (34).

Concerning the use of the compression in DVT patients, both, the compression class as well as duration of the compression use are also still not precisely defined. In the IDEAL DVT Study (based on the group of 865 patients with DVT), the individualization of the compression treatment duration was proposed. The shortening of the compression use to 6 month therapy in some of the investigated patients (based on the Villalta score assessment) resulted in the same clinical outcome as the continuous 2 year therapy (35).

As a consequence of the data analysis further studies on the compression in PTS prevention are needed with the proper way of PTS assessment. In daily practice, in most of the currently treated DVT patients, the compression is used at least in the acute DVT phase to reduce the swelling and local complains. The role of the compression in the symptomatic chronic venous disease patients seems to be also reasonable and unquestioned. The final recommendations for the compression in PTS prevention should be verified in further clinical studies.

### Anticoagulation in PTS prevention

The use of anticoagulation remains the major way of DVT treatment in the acute as well as follow up phases (8). In some of the patients, the minimum DVT anticoagulant treatment (3 months) has to be prolonged, especially if the risk of DVT recurrence remains significant (8). Considering the described relationship between ipsilateral DVT recurrence and higher PTS occurrence, an avoidance of the thrombosis recurrence in the same extremity seems to be one of the major goals of the proper management algorithm (1, 8). To cope with this, various ways of the pharmacological treatment based on the evaluation of the benefits and risks of anticoagulation have been proposed. Most of the anticoagulant treatment studies in DVT patients focus on venous thrombo-embolism (VTE) recurrence, not on PTS prevention. Some meta-analyses as well as post-hoc evaluations allow the conclusion, that there is a potential influence of at least some of the drugs on a decrease of PTS rate. Comparing the efficacy of the use of oral anticoagulants from the vitamin K antagonist group with low molecular weight heparin (LMWH), the latter seem to have a positive influence on PTS rate reduction at least in some of the performed studies (1, 3, 4). To explain these findings both, potential anti-inflammatory as well as the local thrombolysis stimulating effects of LMWH were suggested [36–40]. A retrospective sub-analysis from the Home-LITE study concerning the patients treated with long term course of tinzaparin in comparison with standard anticoagulation treatment based on the short tinzaparin course and warfarin in iliac DVT patients suggests a lower rate of PTS in tinzaparin group (41). A meta-analysis of 5 studies that reported on total vein recanalization after DVT episodes demonstrated a risk ratio of 0.66 (95% CI 0.57–0.77;  $P < 0.0001$ ) in favor of long-term LMWH (42).

An implementation of the new treatment DVT modalities (including the direct oral inhibitors of factor Xa and factor II) is an important step towards the safe and efficacious DVT treatment. Taking into account the still more and more frequent use of this new therapeutic options in the DVT treatment, the potential influence of these therapies on the PTS occurrence should also be investigated. In the post hoc EINSTEIN DVT/PE study analysis no significant

differences in PTS rate between the standard (warfarin) and rivaroxaban treated patients were found, if comparable groups were evaluated (43). Interesting and encouraging results were obtained in a prospective randomized controlled trial comparing the outcomes of rivaroxaban (61 pts.) or warfarin (39 pts.) treatment after median follow up of 23 months in the proximal DVT episode patients. Using the Villalta score assessment, the PTS was diagnosed in 49% patients treated with warfarin and in 25% of the patients treated by rivaroxaban [ $P = 0.013$ , OR for PTS development in warfarin group 2.9 (1.2 – 6.8)] (44). To get a stronger evidence, the promising results of this study should be confirmed in larger group studies and observations.

### Open vein concept – local thrombolysis in proximal DVT treatment and PTS prevention

The “open vein concept” with the early vein lumen patency restoration in the proximal DVT patients suggests the possibility of the PTS prevention by the means of the early thrombus removal (45). Historically, the possibility of the rapid vein lumen restoration in DVT patients was proven in the patients that underwent venous surgical thrombectomy. Currently invasive acute proximal DVT treatment, in most of the cases, is performed as local catheter directed thrombolysis or pharmaco-mechanical methods (46–51). Despite the technical progress in the procedure performance as well as encouraging reports concerning the prospective observation of the case series, the efficacy of this treatment modality in term of PTS prevention remains questionable. In the CAVENT randomized controlled trial, a reduction of PTS rate of 14.4% was observed (47). In this study 209 patients with ilio-femoral DVT were enrolled and randomized to the groups treated by catheter directed thrombolysis (CDT) with rtPA administration or to the standard anticoagulation (189 patients were followed up). In the recently published ATTRACT trial results, 337 patients were randomized to the local thrombolysis group (CDT or pharmaco-mechanical) and 355 patients to the standard anticoagulation treatment (51). In the study cohort (patients with proximal DVT including also ilio-femoral DVT) the rate of PTS (assessed by the means of the Villalta score) was 46.7% in the thrombolysis arm and 48.2% in anticoagulation group ( $p = 0.56$ ) with higher rate of the major bleedings in the patients treated by thrombolytic treatment (1.7% vs 0.3%;  $p = 0.049$ ). New published data with further analyses of ATTRACT results, regarding the group of the patients with DVT limited to the ilio-femoral segment (52). In this subpopulation the local thrombolysis was associated with a reduced rate of moderate and severe PTS (Villalta > 9) occurrence after 24 months of follow up (thrombolysis: 18% vs anticoagulation: 28%;  $p = 0.021$ ). Severe PTS (Villalta > 14) in this cohort was reduced from 15% in the anticoagulation group to 8.7% in the thrombolysis treated patients ( $p = 0.048$ ).

Open surgical concepts remain for sure an interesting and valid option in the area of DVT treatment and PTS prevention. However according to the current research results, the real value of this hypothesis in the PTS prevention has to be investigated in further research based on the well projected studies with an implementation of proper and objective PTS criteria. On the other hand, the invasiveness of a thrombolysis treatment and potential risk of bleeding allows the clinical application of this treatment approach only in a limited number of patients.

## CONCLUSION

The successful post-thrombotic syndrome prevention remains still a difficult clinical problem and unanswered question in many of the research areas. Despite the presence of several PTS predictive models as well as the knowledge concerning some of the PTS predictive factors, we are probably still not able to predict the final outcome of the DVT episode in the individual deep vein thrombosis patient. Further studies are required with the urgent need of new, objective PTS criteria and standardized way of PTS evaluation.

## Conflict of interest

The authors declare that they have no conflict of interest.

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