New perspectives for prevention of the post-thrombotic syndrome

Paolo Prandoni

Arianna Anticoagulazione Foundation, Bologna, Italy

ABSTRACT

While on conventional anticoagulation, up to 50% of patients with one or more episodes of proximal deep vein thrombosis (DVT) can develop post-thrombotic (PTS) manifestations. The potential strategies for PTS prevention are the treatment of acute DVT with catheter-directed thrombolysis (CDT), the use of elastic compression stockings (ECS) and that of the direct oral anticoagulants (DOAC) in place of vitamin K antagonists (VKA) for the initial and long-term treatment of DVT. Based on the results of three randomized clinical trials, CDT cannot be recommended on a routine basis because of its invasiveness, the associated risk of major bleedings and the uncertainty about its efficacy. According to the results of a placebo-controlled randomized clinical trial, ECS are no longer recommended for PTS prevention on a routine basis. However, based on the results of a recent subanalysis of a prospective cohort study, patients with residual vein thrombosis and/or popliteal valve reflux at three months are likely to benefit from ECS for at least six months. Finally, following the demonstration that the inadequacy of VKA therapy plays a key role in the PTS development, several retrospective and prospective studies have shown that the use of DOACs for the initial and long-term treatment of DVT in place of VKAs reduces the risk of PTS by approximately 50%. In conclusion, the availability of DOACs and the potential of ECS in selected patients with proximal DVT are expected to play a key role for decreasing the rate and the severity of PTS in the forthcoming years.

EPIDEMIOLOGY AND RISK FACTORS

Post-thrombotic syndrome (PTS) is a chronic complication of deep vein thrombosis (DVT) of the lower extremities that develops in a substantial proportion of patients following one or more episodes of proximal DVT despite adequate anticoagulant treatment.[1,2] PTS manifestations range from mild symptoms to debilitating complaints, such as skin induration, intractable edema and skin ulcers. They are generally aggravated by standing or walking, while tend to improve with rest and leg elevation. Although PTS may occur within two years after DVT, in most patients they develop within the first six months.[1,2] They are expected to increase the health care costs, the total per-patient cost being almost 50% higher than that of DVT patients without PTS.[3]

Based on the results of several prospective cohort studies, the development of long-term sequelae arising after an episode of proximal DVT is expected to occur in 40-50% of patients receiving conventional anticoagulation, and in approximately 8-10% is serious enough to severely impair patients' quality of life.[1,2,4,5]

Factors that were generally found to be associated with an increased rate of PTS at time of presentation with an acute DVT are elderly age, varicose veins, obesity and the involvement of the most proximal venous segments; and those arising during the follow-up the persistence of residual vein thrombosis, the development of popliteal valve reflux, the inadequacy of anticoagulant therapy, and the development of recurrent ipsilateral DVT.[6] Additionally, baseline inflammatory markers elevation (such as C-reactive protein and interleukin-6) at the time of the index DVT, as well its persistency over the subsequent months have been found to predict the development of PTS.[7] In recent years, two scores have been derivate and validated, which have the potential to predict the development of PTS: the SOX PTS model generated from the SOX study,[8,9] and the IDEAL PTS model, generated from the IDEAL DVT study.[10,11] They are displayed in Tables 1 and 2, respectively. At present, however, the value of these scores is still uncertain, as are their implications for clinical practice.

The potential strategies for PTS prevention are essentially three: i) the treatment of acute DVT with catheter-directed thrombolysis (CDT); ii) the use of elastic compression stockings (ECS) in order to counteract the

Correspondence: Paolo Prandoni, *Arianna Anticoagulazione* Foundation, Via P. Fabbri 1/3, 40138 Bologna, Italy.
Tel.: +39.340.2808202
E-mail: prandonip@gmail.com

Kew words: Post-thrombotic syndrome, Deep vein thrombosis, Catheter-directed thrombolysis, Elastic compression stockings, Anticoagulation, Vitamin K antagonists, Direct oral anticoagulants.

Conflict of interest: The author declares no potential conflict of interest.

Funding: None.

Received for publication: 10 February 2022.
Accepted for publication: 8 March 2022.

Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2022; 1:20
doi:10.4081/btvb.2022.20

venous hypertension generated by residual vein thrombosis (RVT) and/or popliteal valve reflux (PVR); and iii) the use of the novel direct oral anticoagulants (DOAC) in place of vitamin K antagonists (VKA) for the initial and long-term treatment of DVT.

CATHETER-DIRECTED 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. Whether, however, this strategy is associated with a favorable benefit/risk ratio is still uncertain. So far, the results of three randomized controlled clinical trials addressing the value of CDT have been published. In the ATTRACT study, by far the most robust investigation, approximately 800 patients with proximal DVT were randomized to receive conventional anticoagulation alone or preceded by CDT.[12] There was no difference at all between the two study groups in terms of PTS development, as assessed with the Villalta scale, after two years. By converse, the use of CDT was associated with a significantly higher incidence of major bleeding complications. However, in a prespecified subgroup analysis the incidence of moderate/severe PTS was found to be lower in the subgroup of patients with ilio-femoral thrombosis.[13] The results of the ATTRACT study are consistent with those of two additional smaller clinical trials, the CAVENT[14,15] and the DUTCH CAVA,[16,17] and suggest that CDT cannot be recommended on a routine basis because of its invasiveness, the associated risk of major bleedings and the uncertainty about its efficacy. At present, it can be considered only in patients with threatening clinical presentation provided the ilio-femoral tract is involved and the bleeding risk is low, in centers where adequate expertise and resources are available.[1,2]

ELASTIC COMPRESSION STOCKINGS

ECS have been used for decades in patients with DVT with the aim of counteracting the venous hypertension generated by the vascular disorder and reducing leg edema. In two small, randomized studies, published 20 years ago, the use of below-knee stockings for at least two years was found to reduce by approximately 50% the incidence of PTS.[18,19] By contrast, a recent large, double-blind randomized clinical trial (the SOX study) failed to confirm the advantage of stockings.[20] Indeed, after two years of follow-up there was no difference at all between the two study groups (each of them including approximately 400 patients) in terms of PTS development, as assessed with the Ginsberg index and with the Villalta scale. Although, due to the unexpectedly low compliance (lower than 50%), the conclusions of this study have generally been criticized, most international guidelines do no longer recommend the routine use of ECS besides conventional anticoagulation in patients with proximal DVT.[1,21] How-

Table 1. SOX PTS score for the prediction of PTS. A score ≥4 identifies patients at a higher risk of PTS.

Features	Score
BMI >35 kg/m2	2
Iliac vein involvement	1
Moderate (score 5-9) Villalta score at DVT presentation	1
Severe (score >10) Villalta score at DVT presentation	2

PTS, post-thrombotic syndrome; DVT, deep vein thrombosis.

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

Features	Baseline score	Score at six months
Age >56	2	1
BMI >30 kg/m2	2	1
Varicose veins	4	3
Smoking	1	1
Residual vein thrombosis	-	1
Female gender	1	-
Ilio-femoral DVT	1	-
Provoked DVT	1	-
Previous DVT	1	-

PTS, post-thrombotic syndrome; DVT, deep vein thrombosis.

ever, elastic stockings are still commonly prescribed in clinical practice.[22] In addition, 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,[23] a meta-analysis of all available controlled studies turned out to indicate a trend favoring the use of stockings.[24]

In a systematic review and meta-analysis of 12 investigations, it was concluded that patients with RVT and/or PVR, as assessed with ultrasonography at least six weeks after an acute DVT, exhibit a significantly higher risk of subsequent PTS than those without these ultrasound findings.[25] As each of these abnormalities, both alone and in combination, can generate a longstanding venous hypertension that may be counteracted by the compression therapy, the conclusions of these investigators drew new attention on the potential of ECS in these two subgroups of patients.

Therefore, we decided to explore retrospectively the risk of PTS in a broad number of almost 900 patients with proximal DVT, who had been recruited at our Institution between 2003 and 2009 and were then followed up for three years.[26] In all patients the ultrasound assessment of RVT and/or PVR at three months had been performed using a standardized procedure. Using predefined criteria, patients were classified as those who used proper stockings for at least 70% of daily time for at least one year after the thrombotic episode ('stockings' group), and those who did not ('no stockings' group).[27] The two groups were virtually comparable in terms of baseline characteristics, risk factors of venous thrombosis and risk factors of PTS. The findings were interesting. Indeed, while in patients with RVT and/or PVR the risk of PTS was high and was remarkably reduced by the proper use of stockings, in those free from vascular damage the risk of PTS was lower and not impacted using stockings. Of the two vascular abnormalities, RVT was the one that impacted the study results most.[27]

Accordingly, the ultrasound detection of RVT (especially if associated with PVR) three months after an acute proximal DVT has the potential to identify patients at a higher risk of developing PTS and of benefiting from ECS.

THE USE OF THE DIRECT ORAL ANTICOAGULANTS FOR THE INITIAL AND LONG-TERM TREATMENT OF PROXIMAL DEEP VEIN THROMBOSIS

Among factors associated with an increased risk of PTS development, the inadequacy of VKA treatment is likely to play a key role in the development of PTS. Indeed, based on the results of a Dutch-Italian investigation conducted a few years ago, PTS is expected to develop three times more frequently in patients whose INR is below 2.0 in more than 50% of time during the first three months of anticoagulation.[28] By converse, the use of low-molecular-weight heparin (LMWH) as a standalone therapy in place of VKAs is associated with a lower risk of PTS, most likely because of its strong anti-inflammatory properties coupled with a more stable anticoagulant effect.[29,30] A cohort study addressing value of an initial 3-4 week period of LMWH therapy before shifting to conventional DOAC treatment in patients reputed at a higher risk of PTS is currently ongoing.[30]

The DOACs have now become commercially available worldwide. 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.[31] In addition, they have recently been found to restore the vein patency more rapidly than VKA.[32] Recently, the results of a prospective multicenter Italian study have been published. The rate of PTS over a 2-year follow-up was calculated in more than 300 patients who had been treated with DOACs (mostly rivaroxaban) and was compared with that found in a historical cohort of more than 1000 patients who had been treated with VKAs and had been followed-up over time using an identical approach.[26] After adjusting for several unavoidable differences between the two cohorts, DOACs were found to decrease by more than 50% the risk of overall and severe PTS over VKAs.[33] According to the results of a recent meta-analysis of seven mostly retrospective investigations addressing the role of rivaroxaban and warfarin for prevention of PTS, the incidence was found to be significantly lower among rivaroxaban recipients.[34] The difference was not only statistically significant but also clinically relevant, as it involved not only the rate of mild and moderate PTS, but also that of the most severe manifestations and that of skin ulcers.

In addition to conferring a more stable anticoagulation and to restoring the vein patency more quickly than the VKA, DOACs are expected to prevent the long-term recurrences in a wide spectrum of patients with VTE. Indeed, based on the results of the Einstein Extension and Einstein Choice studies, rivaroxaban in either conventional or low doses is likely to protect from the risk of recurrent DVT most DVT patients, virtually all but those with major trauma/surgery.[35] These results are consistent with those shown by apixaban in the Amplify Extension study.[36] As recurrent ipsilateral DVT is by far the strongest marker of PTS development,[6] the long-term protection against DVT recurrences conferred by low-dose DOAC in a wide spectrum of DVT patients is expected to result in a substantial decrease of PTS development in comparison to the discontinuation of anticoagulation (as it was the case in the majority of VTE patients when VKAs were the only available resource).

CONCLUSIONS

In conclusion, the availability of DOACs for the initial and long-term treatment of DVT and the potential of ECS in selected patients with proximal DVT are expected to play a key role for decreasing the rate and the severity of PTS in the forthcoming years.

REFERENCES

1. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation 2014;130:1636-61.
2. Visonà A, Quere I, Mazzolai L, et al. Post-thrombotic syndrome. Vasa 2021;50:331-40.
3. Guanella R, Ducruet T, Johri M, et al. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost 2011;9:2397-405.
4. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
5. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 2008;149:698-707.
6. Rabinovich A, Kahn SR. The postthrombotic syndrome: current evidence and future challenges. J Thromb Haemost 2017;15:230-41.
7. Rabinovich A, Cohen JM, Cushman M, et al. Inflammation markers and their trajectories after deep vein thrombosis in relation to risk of postthrombotic syndrome. J Thromb Haemost 2015;13:398-408.
8. Rabinovich A, Ducruet T, Kahn SR. Development of a clinical prediction model for the postthrombotic syndrome in a prospective cohort of patients with proximal deep vein thrombosis. J Thromb Haemost 2018;16:262-70.
9. Rabinovich A, Gu CS, Vedantham S, et al. External validation of the SOX-PTS score in a prospective multicenter trial of patients with proximal deep vein thrombosis. J Thromb Haemost 2020;18:1381-9.
10. Amin EE, Ten Cate-Hoek AJ, Bouman AC, et al. Individually shortened duration versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome: a cost-effectiveness analysis. Lancet Haematol 2018;5:e512-9.
11. Amin EE, van Kuijk SMJ, Joore MA, et al. Development and validation of a practical two-step prediction model and clinical risk score for post-thrombotic syndrome. Thromb Haemost 2018;118:1242-9.
12. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-52.
13. Comerota AJ, Kearon C, Gu CS, et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis. Circulation 2019;139:1162-73.
14. Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-8.
15. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016;3:e64-71.
16. Notten P, Ten Cate-Hoek AJ, Arnoldussen CWKP, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. Lancet Haematol 2020;7:e40-9.
17. Notten P, de Smet AAEA, Tick LW, et al. CAVA (ultrasound-accelerated catheter-directed thrombolysis on preventing post-thrombotic syndrome) trial: long-term follow-up results. J Am Heart Assoc 2021;10:e018973.
18. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759-62.
19. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med 2004;141:249-56.
20. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014;383:880-8.
21. Stevens SM, Woller SC, Baumann Kreuziger L, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report - Executive summary. Chest 2021;160:2247-59.
22. Rabe D, Partsch H, Heidl G, et al. Compression treatment in acute symptomatic proximal deep venous thrombosis - Results of a worldwide survey. Phlebology 2021;36:526-34.
23. Mol GC, van de Ree MA, Klok FA, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. BMJ 2016;353:i2691.
24. Subbiah R, Aggarwal V, Zhao H, et al. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. Lancet Haematol 2016;3:e293-300.
25. Dronkers CEA, Mol GC, Maraziti G, et al. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis. Thromb Haemost 2018;118:1428-38.
26. Prandoni P, Lensing AW, Prins MH, et al. The impact of residual thrombosis on the long-term outcome of patients with deep venous thrombosis treated with conventional anticoagulation. Semin Thromb Hemost 2015;41:133-40.
27. Prandoni P, Lensing AW, Prins MH, et al. Elastic compression stockings for prevention of the post-thrombotic syndrome in patients with and without residual vein thrombosis and/or popliteal valve reflux. Haematologica 2022;107:303-7.
28. van Dongen CJ, Prandoni P, Frulla M, et al. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 2005;3:939-42.
29. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. Am J Med 2011;124:756-65.

30. Makedonov I, Kahn SR, Abdulrehman J, et al. Prevention of the postthrombotic syndrome with anticoagulation: a narrative review. Thromb Haemost 2021 Dec 1. doi: 10.1055/a-1711-1263 [online ahead of print].
31. van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968-75.
32. Prandoni P, Ageno W, Mumoli N, et al. Recanalization rate in patients with proximal vein thrombosis treated with the direct oral anticoagulants. Thromb Res 2017;153:97-100.
33. Prandoni P, Ageno W, Ciammaichella M, et al. The risk of post-thrombotic syndrome in patients with proximal deep vein thrombosis treated with the direct oral anticoagulants. Intern Emerg Med 2020;15:447-52.
34. Li R, Yuan M, Cheng J, Yu S, et al. Risk of post-thrombotic syndrome after deep vein thrombosis treated with rivaroxaban versus vitamin-K antagonists: a systematic review and meta-analysis. Thromb Res 2020;196:340-8.
35. Prins MH, Lensing AWA, Prandoni P, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv 2018;2:788-96.
36. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.