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COMMENTARY

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Commentary on the guidelines for the management of chronic venous disorders of the lower limbs: "Prevention of post-thrombotic syndrome" by Andrew Nicolaides et al.

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Commentary on the guidelines brilliantly developed by prof. Andrew Nicolaides and published in International Angiology in 2020 [1], should begin with the definition of post-thrombotic syndrome (PTS), which is a group of common clinical symptoms following deep vein thrombosis (DVT).

The signs and symptoms may come in various combinations, and they affect especially the lower limbs, but also, but much less frequently, the upper limbs. In most of the studies on PTS, the Villalta scale was used to establish the diagnosis (Table 1) [2].

The authors of this comment agree with Dr. Susan Kahn, who believes that it is still impossible to reliably predict, based on an individual assessment, who will develop and who will not develop post-thrombotic syndrome [3]. Therefore, it is important to know the factors that predispose patients to this condition, which is one of the most serious complications of DVT. Table 2 presents risk factors for post-thrombotic syndrome [4–7]. The risk factors of PTS are not yet well understood. Based on the existing evidence, known risk factors can be divided into 2 groups: 1. recognized or probable factors – whose significance has been confirmed or is suggested by the results of some studies, but further research is necessary to finally determine their role; 2. factors that most likely do not increase the risk of PTS — whose significance was excluded in the studies.

In addition, a recently published observational study identified factors that indicated a greater risk of developing venous ulcers in patients with a history of acute DVT.

Table 1. Clinical diagnosis of post-thrombotic syndrome — Villalta scale [2]

Severity of symptoms and signs	Absent	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Signs				
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3
Venous ulcer	0	1	2	3

Diagnosis if > 5 points

It is also impossible to predict when PTS symptoms will appear; the syndrome has been observed many months to several years after the thrombotic episode. The most common symptoms are heaviness, pain, limb swelling, and often trophic changes and ulceration (Figs. 1, 2).

In the general population, DVT occurs in 1–3 out of 1000 people per year. Among these DVT patients,

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Table 2. Risk factor of post-thrombotic syndrome [4–7]

1) Present at the time of the onset of DVT
• Age (risk increases with age)
• BMI (increased BMI or obesity)
• Venous insufficiency before a DVT episode
• Proximal DVT (especially in the iliac or femoral veins)
2) Related to the treatment of acute DVT
• Inadequate anticoagulation therapy (e.g. percentage of time with INR below therapeutic range is > 50%) during the first 3 months of VKA treatment
3) Present after a DVT episode
• Recurrent DVT on the same side
• Persistent DVT symptoms one month after diagnosis
• Persistent thrombus found on ultrasound 3–6 months after DVT episode
• Increased level of D-dimer
Factors that do not increase the risk of PTS
• Gender
• Type of DVT episode (secondary v. idiopathic)
• Congenital thrombophilia
• Duration of anticoagulation therapy

BMI: body mass index; INR: international normalized ratio; VKA: vitamin K antagonist; PTS: post-thrombotic syndrome; DVT: deep-vein thrombosis

20–50% will develop PTS, and 6–10% will have severe PTS [4]. A good demographic and epidemiological example is the practice of family doctors, which in Poland provide care for about 2,000 patients on average, which means 2 patients with PTS annually in this population. The incidence of DVT is comparable in men and women, but depends on age. It is very rarely diagnosed before the age of 20, and after the age of 40, its incidence doubles with each decade. This means that most of the patients are rather elderly people (although often in working age) in whom the symptoms and ailments related to DVT will largely affect the quality of life, limit mobility and social activity, and generate huge expenses related to treatment, which are a heavy burden on the healthcare budget. Thus, protecting patients from the consequences of a lower limb thrombosis is important not only for the individual but for the entire system. Therefore, the importance of this document that contains the latest recommendations for the prevention of DVT should be appreciated.

Evidence is now available that there are many modifiable risk factors that can guide therapeutic strategies to reduce the risk of PTS. Two of them should be highlighted: prevention of venous thrombosis and, when PTS occurs, drug therapy that is appropriately selected and administered for a sufficiently long time.

The best way to prevent PTS is to avoid getting DVT by using appropriate anticoagulant prophylaxis when there is an increased risk of developing this disease. For example, hospitalization significantly increases the risk of venous thromboembolism (VTE) (4.5 cases/1,000

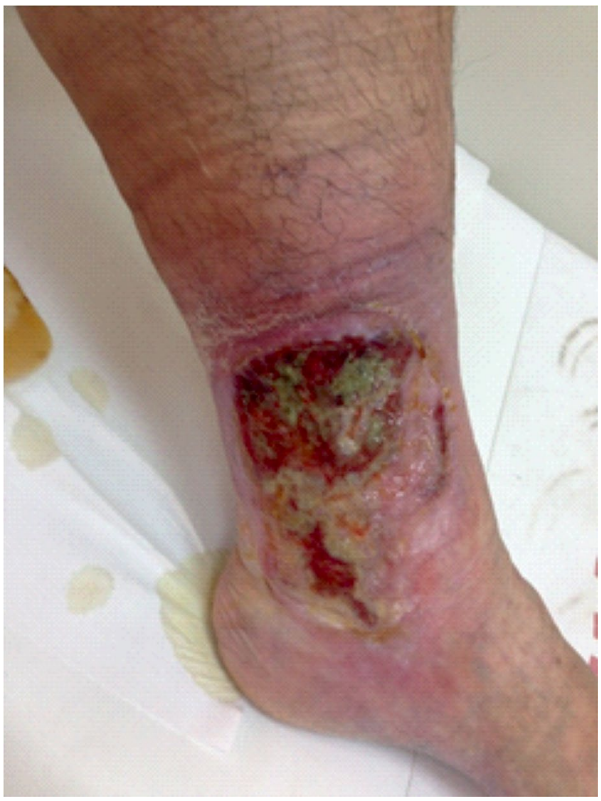

Figure 1. Ulceration in post-thrombotic syndrome

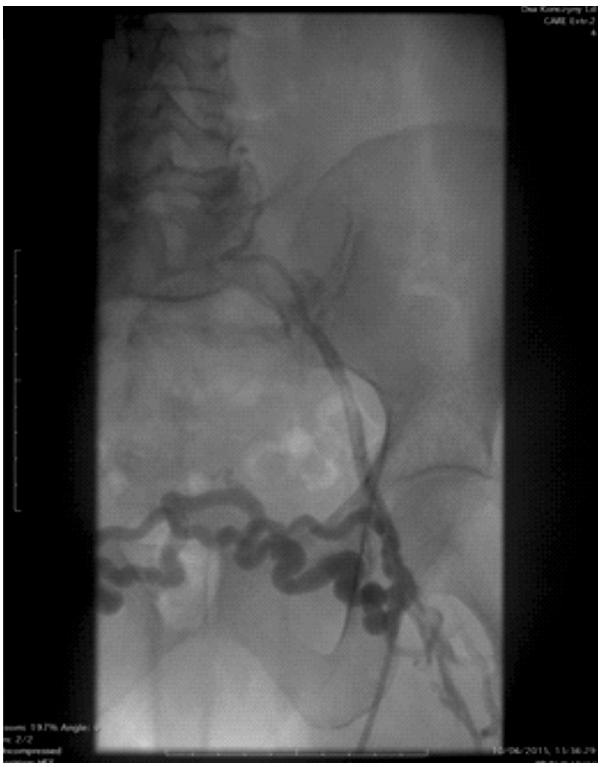

Figure 2. Venography with characteristic collateral circulation bypassing obstructed iliac system

hospital admissions) in patients treated conservatively, and this risk persists for 30 days after hospital discharge. It is also an important factor in increasing the thrombotic risk in cancer patients. Unfortunately, as shown by the results of the ENDORS trial, the use of thromboprophylaxis is far from satisfactory.

VTE risk scales for medical and surgical patients are well described and should be used to define indications for thromboprophylaxis. If thrombosis does occur in the context of PTS, the pathomechanism of its development (unprovoked or caused by a transient thrombotic risk factor) most likely does not play a role [8]. It should also be emphasized that PTS is a consequence of not only symptomatic DVT, but also asymptomatic. Considering the above, properly conducted thromboprophylaxis is of particular importance.

The choice of drugs and the management of patients with venous thrombosis can also have a huge impact on the development of PE. It has been proven that this is the case in patients treated with vitamin K antagonists (VKAs). The risk of developing post-thrombotic syndrome in this group of patients increases if the treatment of DVT during the first 3 months of VKA use is inappropriately conducted. Maintaining the international normalized ratio (INR) at the subtherapeutic level (< 2.0) for more than half of the treatment period increases the risk of PTS by 2.7 times [9]. Another study showed that when the subtherapeutic INR level is maintained for more than 20% of the treatment time, the odds ratio for PTS is 1.84 [95% confidence interval (CI) 1.13–3.01] [10]. Early and more extensive recanalization occurs when DVT is treated with anti-Xa anticoagulants such as low molecular weight heparin (LMWH) or rivaroxaban, which has the effect of reducing the incidence of PTS compared to anticoagulant treatment with VKA.

Currently, attention is being paid to strategies for determining the need and type of extended prophylaxis based on the balance of risk of recurrent DVT (residual thrombosis on ultrasound examination and assessment of D-dimer level in blood or risk scales, e.g. Vienna, HERDOO-2, DASH) versus the risk of bleeding.

It has been shown that recurrent thrombosis in the same limb increases the risk of PTS in various populations up to 10-fold, which is probably caused by further damage to the venous valves or intensification of blood flow disorders [11–14].

Indefinite anticoagulation treatment is recommended for the prevention of recurrent VTE in patients with a first episode of unprovoked proximal DVT of the lower limb or pulmonary embolism who are at low or moderate risk of hemorrhagic complications. If the risk of hemorrhagic complications is high or very high, it is advisable to limit the duration of anticoagulation therapy to 3 months or seek alternatives, such as sulodexide therapy. The study by Luzzi et al. [15] compared sulodexide with acetylsalicylic acid and standard treatment (compression therapy, regular exercise, control of risk factors and body weight) in the prevention of PTS. Over a 5-year follow-up, the risk of developing PTS was lower in the sulodexide group compared to standard therapy and acetylsalicylic acid use (12.7% vs. 18.23% vs. 23.5%, respectively; $p < 0.05$). Other advantages of sulodexide, which classic anticoagulants do not have, are the combination of venoactive and anticoagulant effects, and the prevention of DVT and its recurrence is the most important method of PTS prevention. In all patients treated with long-term anticoagulation, the indications for the continuation of this treatment should be periodically assessed (e.g. every 6–12 months) and further recommendations should be determined individually, after consultation with the patient (the importance of patient involvement in the treatment should be emphasized), taking into account both the risk of recurrence of thrombosis and the risk of bleeding complications [16].

Therefore, while encouraging you to read the guidelines "Management of chronic venous diseases of the lower extremities" by Andrew Nicolaides et al. [1], we would like to draw your attention to the chapter on the prevention of post-thrombotic syndrome, which in our opinion is the most important issue. The guidelines are based on the latest clinical trials and evidence-based medicine (EBM). They emphasize the role of properly used extended pharmacotherapy in the context of the risk of bleeding and the risk of recurrent DVT, which is also aimed at preventing PTS. The authors of this commentary fully support the expert position regarding the use of pharmacotherapy depending on the risk of recurrence and the risk of bleeding.

Patients at high risk of recurrence

1. If the risk of bleeding is low: any anticoagulant drug (VKA, rivaroxaban, apixaban) can be administered.
2. If the bleeding risk is moderate: apixaban.
3. If the risk of bleeding is high: low dose apixaban, sulodexide.

Patients at immediate risk of recurrence

1. If the risk of bleeding is assessed as low, any anticoagulant drug (VKA, rivaroxaban, apixaban) may be administered.
2. If the bleeding risk is moderate: apixaban.
3. If the risk of bleeding is high: low dose apixaban, sulodexide, aspirin.

Patients at low risk of recurrence

In patients with a low risk of recurrence, anticoagulants can be omitted, but if the patient prefers to continue with prophylaxis, the authors recommend aspirin or sulodexide.

Summary

According to the authors of the discussed document, one of the methods of preventing recurrence of thrombosis and the development of post-thrombotic syndrome is extended pharmacotherapy of DVT, based on the assessment of risks of disease recurrence and bleeding.

To reduce the number of relapses, extended VTE therapy with rivaroxaban, apixaban and sulodexide is recommended (evidence level A). In terms of the incidence of PTS in patients on these drugs, the scientific evidence is of lower quality (evidence level B) due to the lack of large randomized controlled trials.

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