

# Clinical significance of recurrent venous thromboembolism

## *Significância clínica de tromboembolismo venoso recorrente*

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### Abstract

Recurrent venous thromboembolism is a significant problem leading to increased morbidity and mortality. It has a high impact on patients' quality of life and imposes a great financial burden on society. Cumulative recurrence has been reported as 40% at 10 years, while the chance of developing postthrombotic signs and symptoms in the lower extremities almost quadruples when ipsilateral. There is also a higher chance of developing pulmonary hypertension. Important factors for recurrence are unprovoked episodes of deep vein thrombosis, malignancy and older age. The evidence for other factors is controversial. Accurate diagnosis and treatment tailored to the patients' history, thrombotic events and risk factors are necessary to optimize management and prevent recurrence.

**Keywords:** Recurrent venous thromboembolism, postthrombotic syndrome, pulmonary hypertension, anticoagulation.

### Resumo

O tromboembolismo venoso recorrente é um problema importante que leva ao aumento da morbimortalidade. Impõe forte impacto à qualidade de vida dos pacientes e grande carga financeira para a sociedade. Acredita-se que a recorrência cumulativa atinja 40% em 10 anos, enquanto que a chance de desenvolver sinais e sintomas pós-trombóticos nas extremidades inferiores quase quadruplica no caso de trombose ipsilateral. Há também uma maior chance do desenvolvimento de hipertensão pulmonar. Fatores importantes para a recorrência são: episódios não provocados de trombose venosa profunda, malignidade e idade avançada. As evidências relacionadas a outros fatores são controversas. Diagnóstico preciso e tratamento adaptado ao histórico dos pacientes, aos eventos trombóticos e aos fatores de risco são necessários para otimizar o manejo e prevenir a recorrência.

**Palavras-chave:** Tromboembolismo venoso recorrente, síndrome pós-trombótica, hipertensão pulmonar, anticoagulação.

### Introduction

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After a first episode of thrombosis, many patients may experience a second thromboembolic event. Pandoni et al.<sup>1</sup> showed that the cumulative incidence of recurrent venous thromboembolism was 11.0% (95% CI, 9.5-12.5) at 1 year, 19.6% (17.5-21.7) at 3 years, 29.1% (26.3-31.9) at 5 years, and 39.9% (35.4-44.4) after 10 years. The incidence of recurrence was significantly higher in patients with unprovoked deep vein thrombosis (DVT) (52.6, 95% CI, 45.6-59.5) compared to those with secondary DVT (22.5, 95% CI, 17.2-27.8). Recurrent DVT has a significant impact on patients' mortality and quality of life. A second episode of DVT exposes patients to pulmonary embolism that can be fatal or increase the chance for pulmonary hypertension. Furthermore, ipsilateral recurrent DVT of the lower extremities has been associated with higher odds of

developing post-thrombotic disease. Therefore, accurate diagnosis and prevention of recurrent DVT have become very important components of current clinical practice and research. This paper analyzes and discusses all the main factors associated with the diagnosis, morbidity and mortality of recurrent DVT.

### Diagnosis

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DVT of the extremities is routinely diagnosed by duplex ultrasound. In patients who have thrombosis of the inferior vena cava (IVC) or iliac veins, other modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) or phlebography are also used. Patients with DVT often present with pain, swelling or signs and symptoms of pulmonary emboli (PE). For patients who develop signs and symptoms of PE, a CT or an MR angiography is

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performed. Recurrent venous thromboembolism (VTE) has been well documented and reported in relation to the previous distribution of DVT.

It has been shown that 30 to 60% of patients develop postthrombotic syndrome within 5 to 10 years of initial DVT, and that the condition is more likely among patients with ipsilateral recurrent DVT.<sup>2</sup> Ipsilateral recurrent DVT was also the most important predictor for CEAP class progression.<sup>3</sup> The CEAP classification system for venous disease allows us to grade the severity and study the natural history of VTE.

### Imaging

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Criteria for diagnosing DVT include: partially compressible or incompressible vein, echogenic material within the vein, filling defect on color duplex or absence of Doppler signal. Duplex ultrasound can also distinguish acute from chronic thrombosis. In chronic DVT, the thrombotic venous segments may have reduced diameter with bright echoes are within the lumen because of old thrombus or scar tissue. There is usually partial recanalization with filling defects, wall thickening and collateral veins may be present. In acute DVT, the vein is distended and the lumen is partially compressible and echolucent, while the vein wall is smooth. The presence of reflux in the deep veins with previous thrombosis is also indicative of chronic DVT.<sup>4</sup> The cutoff value for reflux in the common femoral, femoral, and popliteal veins is 1 s and 0.5 s for the calf deep veins.<sup>5</sup>

Recurrent DVT is also diagnosed with duplex ultrasound imaging. The diagnosis of recurrent thrombosis uses the following criteria: extension of thrombus of greater than 9 cm, incompressibility of vein segment that has been previously recanalized and enlargement of thrombus thickness greater than 4 mm.<sup>6,7</sup>

An MRI of the lower extremities is also used for imaging the lower extremities. This is an expensive yet non-invasive test with sensitivity of 87, 100 and 100%, respectively, for calf, thigh, and pelvic DVT with corresponding specificities of 97, 100 and 95%.<sup>8</sup> MR-venography (MRV) can identify vein wall inflammatory changes and may differentiate acute from chronic thrombus while providing information about the surrounding tissues.<sup>9</sup> Froehlich et al. showed how MRV can determine thrombus age by measuring the signal intensity at the periphery and the center of the thrombotic vein at the level of maximum thrombus. This study described the characteristic "bull's eye" sign in an acute thrombus that decreased chronically.<sup>10</sup>

### Post-thrombotic syndrome

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Post-thrombotic syndrome is characterized by chronic pain, swelling, heaviness, itching, burning sensation, skin discoloration, venous claudication and in the more severe cases presents with venous ulcers. Patients present with venous claudication when they feel pain when walking despite normal ankle brachial index. The most common causes of post-thrombotic syndrome (PTS) are reflux, obstruction or a combination of both. Patients with both reflux and obstruction have more skin damage than those who have either of the two.<sup>11</sup> Furthermore, obstructions persisting after 6 months from the thrombotic event were important predictors of PTS, whereas the presence of venous reflux was not.<sup>12</sup> Predictors of poorer long term outcomes for PTS included venous thrombosis of the common femoral or iliac vein, higher body mass index, older age, female sex, and increased PTS manifestation within the first month after venous thrombosis.<sup>13,14</sup>

Patients who have had thromboses in more than one venous segment had higher prevalence of recurrent thrombosis and a more advanced form of PTS.<sup>11</sup> Patients with ipsilateral recurrence were more likely to have partial recanalization, reflux, and more diseased venous segments than patients with contralateral recurrence.<sup>3</sup> Calf thrombosis in patients with proximal DVT led to the highest rate of PTS prevalence.<sup>11</sup>

### Pulmonary hypertension

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The most feared complication of acute DVT is PE followed by chronic thromboembolic pulmonary hypertension (CTEPH). Patients that presented with PE were more likely to develop recurrent PE than patients with DVT alone (69/122 vs. 61/250, respectively; RR, 2.32; 95% CI, 1.77 to 3.03).<sup>1</sup> CTEPH is characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries resulting in pulmonary hypertension and progressive right heart failure. Patients with CTEPH present with progressive dyspnea on exertion, hemoptysis and signs of right heart dysfunction including fatigue, palpitations, syncope, or edema. First diagnostic test includes ventilation perfusion scan, and experts agree that a normal ventilation-perfusion scintigram practically rules out the presence of CTEPH.<sup>15</sup> Other imaging modalities include echocardiography, CT, MRI, and pulmonary angiography.

The data on the value of the mean pulmonary artery pressure and the progression of pulmonary hypertension is conflicting. However, patients who present with

persistent pulmonary hypertension after PE will have poorer disease outcomes despite adequate anticoagulation. These patients are at a higher risk of death from right heart failure if untreated.<sup>16</sup>

### **Prevention and extent of anticoagulation**

Though several studies have shown the detrimental impacts of recurrent DVT, improving the long-term prognosis of patients with acute VTE remains a challenging task. Patients with deep venous thrombosis are usually treated with an initial course of heparin (5 to 10 days) followed by 3 to 6 months of oral anticoagulant therapy.<sup>2</sup> For patients with a first episode of DVT secondary to a transient (reversible) risk factor, long-term treatment with a vitamin K antagonists (VKA) for 3 months is recommended over treatment for shorter periods; and for patients with a first episode of idiopathic DVT, VKA treatment for at least 6 to 12 months is recommended.<sup>17</sup> This treatment regimen reduces the risk of short-term thromboembolic complications to approximately 5%.<sup>2</sup>

The number of VTE related long-term complications could be reduced by more than half if thromboprophylaxis was universally applied to patients at risk.<sup>18</sup> Thromboprophylaxis is used according to the American College of Chest Physicians antithrombotic and thrombolytic therapy guidelines.<sup>19</sup> Furthermore, heart failure, pneumonia, respiratory failure and cancer patients represented the population that most benefited from VTE prophylaxis. Low quality treatment with vitamin K antagonists was associated with the recurrence of PTS in patients with DVT.<sup>20</sup>

For patients with symptomatic DVT, compression stockings can decrease the frequency of PTS by 50%, and have the potential to help patients either remain stable or improve during long-term follow-up.<sup>14,21</sup>

Duplex ultrasonography has been universally accepted as the primary diagnostic test for DVT. The persistence of residual thrombosis as shown by repeated ultrasonography is an independent risk factor for recurrent VTE and may modify the extent of anticoagulation.<sup>22</sup> Indications for follow-up venous duplex scanning include examination of proximal veins in patients with initial negative examination, isolated calf thrombosis, recurrent symptoms, and completion of anticoagulation therapy.<sup>23</sup>

### **Mortality**

VTE is a significant predictor of death, with patients dying from PE, cancer or other thrombotic events. A

prospective study showed that survival from recurrent VTE after 8 years was 70.2% (CI, 64.7% to 75.6%). Of the 29.8% of patients who died, 11.5% were attributed to PE.<sup>2</sup> A decade later, the same group in a large prospective study of 1628 patients with 10 years of follow-up revealed similar findings.<sup>1</sup> It is important to note that patients who had PE as their initial event have a higher mortality rate than those presenting with DVT. Mortality was significantly increased at 1-month follow-up for patients who initially presented with PE (13.0%) compared to those with DVT (5.4%), and the difference persisted at 3 years (35.3% vs. 29.6%).<sup>24</sup>

### **Limitations of current studies**

Some studies have indicated the importance of ilio-femoral involvement on increased recurrence and PTS. However, there has been no detailed analysis of all the venous segments alone or in combination. The weight of each risk factor and the effects of the various risk factors have not been studied. The optimal duration and dosing of anticoagulation and the effect of thrombolysis have not been adequately studied either. Rigorous inclusion/exclusion criteria have not been used in studies with VTE events, making it difficult to translate and apply the findings for all patients.

Other limitations include incomplete data collection on anticoagulation management with particular emphasis on INR levels and patient compliance. The incidence and prevalence of CTEPH is unknown due to the lack of prospective studies in which patients with PE are followed at long term. The true mortality rate from PE is also unknown, since most patients do not undergo autopsies.

### **Future perspectives**

Case fatality rates associated with PE and rates of recurrent VTE remains unacceptably high. Although important advances in the management of VTE have been made, there still remains considerable room for improvement. Long-term multicenter studies are required to determine risk factors for the development of CTEPH and for the implementation of preventive strategies.

Preventing DVT recurrence and the daily use of compression stockings can reduce the risk of PTS. The role of thrombolysis in preventing PTS has not been established but trials are underway to address this important question. Research is also underway to identify biological markers that may predict the risk of PTS.

Further work must be done to investigate the association between inflammation and PTS that could identify

new therapeutic targets for preventing PTS. Long term-randomized trials are required to monitor the recanalization and to assess the risks, benefits and duration of anticoagulation therapy to prevent VTE recurrence.

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