

## Editorial Focus

# VTE recurrence in patients with inherited deficiencies of natural anticoagulants

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Venous thromboembolism (VTE) is a serious clinical condition manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Patients with VTE have a considerable risk of recurrent VTE that persists for many years (1, 2). In a population based cohort study, Heit et al. (1) found an overall cumulative percentage of VTE recurrence at 180 days, 1 and 10 years of 10.1%, 12.9%, and 30.4%, respectively. In another recent prospective cohort study, Prandoni et al. (2) reported, in patients with a first episode of VTE followed for eight years after oral anticoagulant therapy (OAT) withdrawal, a cumulative incidence of recurrence of 17.5% after two years, 24.6% after five years, and 30.3% after eight years. OAT is effective in reducing the VTE recurrence rate. However, anticoagulant treatment is associated with an increased risk for bleeding complications (3). Thus, anticoagulation has to be discontinued when the benefit of treatment no longer outweighs its risks and this clearly depends on the estimated risk of recurrence. The optimal duration of OAT is established, either after a first episode of VTE, in patients with a transient or with a persistent risk factor for VTE with an average risk of bleeding.

Patients with a persistent risk factor for VTE had a high risk of recurrence. In patients with cancer, the risk of recurrent VTE after stopping anticoagulant therapy is as high as 10% to 20% in the first year, particularly among those with metastatic disease or among those who received concurrent chemotherapy (2, 4). Thus, in view of the persistently high risk of VTE recurrence, a prolonged anticoagulant treatment is currently recommended in patients as long as the cancer remains active.

Conversely, in patients with major reversible risk factor such as surgery, immobilization or trauma, the risk of recurrence is relatively low (5), and to stop anticoagulant therapy after three months of treatment appears to be a reasonable option. On the other hand, the optimal duration of OAT in patients with a first unprovoked episode of VTE is still uncertain, and recent guidelines of the American College of Chest Physician suggested to carefully assess the potential risks and benefits of long-term OAT in each patient (6).

Recently, several studies have assessed the role of some individual features evaluated at the end of conventional anticoagu-

lant treatment as risk factors for recurrence (7, 8). The main aim of this approach was to identify those patients with unprovoked VTE who could benefit from extended anticoagulant treatment. In a randomized controlled study, Palareti et al. showed that patients one month after discontinuation of anticoagulation with an abnormal D-dimer level had a significantly higher incidence of recurrent VTE compared to patients with normal D-dimer, and that resumption of anticoagulation was effective in reducing thromboembolic complications in these patients (7). In a prospective cohort study on 313 consecutive symptomatic outpatients with proximal DVT, Prandoni et al. showed that persistence of residual venous thrombosis at follow-up visits was associated with an increased risk VTE recurrence (8). Several studies and a meta-analysis have revealed that men have at higher risk of recurrence than women (9) and first manifestation of thrombosis as PE seems to be associated with an increased risk of VTE recurrence (10).

During the last decade several abnormalities in the coagulation system have been shown to be associated with an increased risk of thrombosis. Their impact on the recurrence rate has been the focus of several clinical studies. Factor V Leiden and the prothrombin G20210A variation, the commonest inherited risk factors for thrombosis, are associated with an increased risk of VTE recurrence (11). However, the magnitude of the risk conferred by the presence of one of these risk factors is modest and not sufficient to warrant long-term anticoagulation. Inherited deficiencies of natural anticoagulants antithrombin, protein C, and protein S are present in less than 10% of VTE patients (12). Patients with these deficiencies are considered at higher risk for VTE (13). On the other hand, only few studies with a limited number of included patients have assessed the risk of recurrence associated with these thrombophilic abnormalities (14, 15). In these studies, the risk of recurrence in patients with first VTE and a thrombophilic defect and in patients without a thrombophilic defect was similar. However, these studies also included patients with other thrombophilic defects such as factor V Leiden, prothrombin G20210A mutation and included a relatively small number of patients with deficiencies of natural anticoagulants.

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In a study published in this issue of *Thrombosis and Haemostasis*, Brouwer et al. showed that patients with deficiencies of natural anticoagulants had a high risk of VTE recurrence during follow-up (16) and, although these results should be handled with caution due to the lack of a proper control group, this risk appeared to be increased in comparison to the annual risk of recurrence in the general VTE population. Different results among the studies may be due to differences in inclusion and exclusion criteria. Familial protein S deficiency type III was excluded from analysis in the study performed by Brouwer et al. because it was

not identified as a risk factor for thrombosis (17). Furthermore, individuals from thrombophilic families tend to have a much higher risk probably attributable to the concomitant presence of other risk factors within these families (18).

Therefore, even if not conclusive, these new data reinforce the need to test patients with unprovoked vein thrombosis for the presence of deficiencies of natural inhibitors in concomitance with other potential risk factors for recurrence to properly assess the VTE risk of recurrence to correctly inform each patient and to individualize future preventive strategies.

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