Should the commonly accepted definition of "unprovoked venous thrombembolism" be revisited?

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Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) of the lower limbs and pulmonary embolism (PE), occurs with an incidence of approximately one per 1,000 annually in adult populations (1). The onset of VTE may be provoked in some individuals by the exposure to a number of major risk factors including surgical procedures, prolonged immobilisation, trauma or fractures. In the presence of such risk factors, which are most of the times identified in hospitalised patients, adequate thromboprophylactic strategies are highly recommended, since PE remains the most common preventable cause of in-hospital death. To improve the correct identification of patients requiring prophylaxis and to offer the optimal prophylactic treatment, additional information on the presence of concomitant risk factors such as advanced age, obesity, underlying inflammatory or infectious diseases, or cancer, to name a few, is usually collected.

VTE also shows a considerable long-term risk of recurrences. Prospective cohort studies have found an overall cumulative incidence of recurrent VTE of about 17% after two years, and up to about 30% after 8–10 years (2, 3). This risk of recurrence is highly heterogeneous, and the definition of the individual risk is generally based on the identification of triggering factors. It is usually accepted to stratify patients based on the presence of permanent provoking factors (e.g. cancer) or transient provoking factors which commonly include, in addition to those mentioned above, pregnancy and the use of oral contraceptives. This simple categorisation of VTE patients is useful since it offers an easy stratification of the different risks of long-term recurrence of the disease: after one year from stopping secondary prevention with anticoagulant therapy, the cumulative incidence of recurrent VTE is expected to be low if the event was associated with a transient risk factor (4) and very high if the event occurred in association with cancer (5). Although this categorisation is practical and is proposed by international clinical guidelines on the optimal duration of secondary prevention of VTE (6), it presents some clear drawbacks. First, within the group of patients with VTE secondary to major, transient risk factors, the risk of recurrence varies between patients with a non-surgical risk factor and patients with a surgical risk factor (4), thus suggesting the need for a more detailed definition of the individual risk despite the transient nature of the provoking factor. Second, this categorization leaves a non-negligible proportion of patients defined as "unprovoked" or "idiopathic", ranging between 25% and 50% or more, according to the design of the studies (7–9). This large population has an estimated risk of recurrence which lies between that of the low risk categories and that of the very high risk groups, such as patients with cancer (10), but clearly presents a high heterogeneity of individual risk profiles, thus suggesting the need to improve patients' stratification.

Because VTE is best understood as a multicausal disease resulting from the complex interaction between congenital and acquired risk factors (11), we believe there is still room to improve this categorisation of VTE patients by including in the individual assessment some additional, non-major risk factors, as we do when deciding prophylactic strategies in hospitalised patients.

Several of these risk factors have in fact been associated with the onset of VTE, including increasing age (12), traditional cardiovascular risk factors and the metabolic syndrome (13, 14), smoking (15), endocrine disorders (16, 17), and mild thrombophilia (18), among others. Because of their rather high prevalence in the general population, the concomitant action of these minor risk factors may also be important in the pathogenesis of VTE and in the definition of the risk of recurrence.

In this issue of Thrombosis and Haemostasis, Tichelaar et al. performed an extensive and timely updated systematic research of the literature in which they evaluated the role of several infective and inflammatory diseases as risk factors for VTE (19). The authors were able to summarise the results of 31 studies of general good quality. The results of this study showed that the presence of some of these diseases including inflammatory bowel disease, ANCA-associated vasculitis, infections and, more specifically, pneumonia and urinary tract infections, are associated with an increased risk of venous thrombosis, and the results were consistent across different studies.

As expected, this association was strongest when the time between the exposure and the outcome was short, that is when the inflammatory or infectious disease was experienced recently or while an inflammatory or auto-immune disease was active (flare-up).

An association was also observed between human immunodeficiency virus (HIV) infection and VTE. However, whether this association depends on the infection itsself or it is due to the use of highly active anti-retroviral therapy or to the high prevalence of other traditional risk factors in these patients remains to be established (20). On the other hand, the role of other

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Received: March 13, 2012
Accepted: March 13, 2012
Prepublished online: ■■
doi:10.1160/TH12-03-0164
Thromb Haemost 2012; 107: ■■■

potential risk factors including sarcoidosis, coeliac disease, or cytomegalovirus and Chlamydia infections was less clear since the results of single studies were more conflicting. Although some effects of cytomegalovirus or other agents on the coagulation system have been described (21), their association with VTE remains to be established.

The results of the study by Tichelaar et al. are clinically relevant because they provide additional evidence on the role of minor and less known risk factors on the pathogenesis of VTE. If on the one hand the need for primary prophylaxis of VTE in patients with acute infections or active chronic inflammatory diseases is well established in the concomitant presence of major risk factors such as immobilisation, surgery, or delivery with caesarean section, the role of these and other minor risk factors on the risk of recurrent VTE is less clear. However, obesity has been found to be associated with an increased risk of recurrence (hazard ratio 1.6, 95% confidence interval [CI] 1.1–2.4) (22) and a recent study on more than 1,300 patients with a first episode of unprovoked VTE found a higher risk of recurrence in patients with inflammatory bowel disease as compared to patients without (relative risk 2.5, 95% CI 1.4–4.2) after adjustment for age, sex, factor V Leiden mutation, prothrombin mutation, factor VIII level, duration of anticoagulation and body mass index (23).

These observations are biologically plausible. Minor risk factors that are transient in nature, such as an acute infection, induce a temporary hypercoagulable state which contributes to the index event, but which disappears over time reducing the individual risk of recurrence. This risk may rise again in case of relapsing infections, thus suggesting the need for adequate thromboprophylaxis only during this time frame. Conversely, conditions that are associated with a persistent inflammation such as chronic inflammatory disorders, but also such as obesity, may expose patients to a persistent hypercoagulable state and thus to a persistently increased risk of recurrences. For these reasons, we believe that a careful evaluation of all minor risk factors is needed also when deciding the optimal duration of secondary prevention after a first episode of VTE and that future studies should help to revise the current definition of "unprovoked" or "idiopathic" VTE to improve the accuracy of treatment strategies.

Conflicts of interest
None declared.

This editorial reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

Editorial on Tichelaar et al. Thromb Haemost 2012; 107: ■■■

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