Identifying Risk Factors for Venous Thromboembolism

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Our understanding of risk factors associated with the development of venous thromboembolism (VTE) has increased steadily over the past 20 years. In the 1980s, the development of VTE was conceptualized in the context of the factors in Virchow’s classic triad that he believed led to venous thrombosis. These factors were injury to the endothelium, alteration in blood flow (particularly stasis/immobility for venous thrombosis), and activation of blood coagulation.1 Patients who had a disease or condition that included one of these factors were considered to have a predisposing condition,2 whereas patients without any of these factors were categorized as having an idiopathic venous thrombosis. In the 1980s, the principal terms used to categorize acute venous thrombotic events were idiopathic and secondary venous thromboembolism. Gradually the term unprovoked, first coined by Kearon,3 began to be used instead of idiopathic, and provoked was used in place of secondary. More recently, provoking risk factors have been divided into temporary provoking risk factors and persisting provoking risk factors, although there is no strict definition of what constitutes a temporary or transient risk factor. Practically speaking, clear examples of transient provoking risk factors include a lower-extremity fracture, major surgery, and long-distance travel. However, the notion that a clinician can easily identify a provoking risk factor becomes less certain as the time between the possible provoking event and onset of acute VTE increases. Is surgery a provoking risk factor when an acute VTE develops 90 or 120 days after an operation? The best examples of a persisting provoking VTE risk factor are an active medical diseases such as cancer, inflammatory bowel disease, or nephrotic syndrome, and a chronic medical condition such as immobility or a prior history of VTE.

Accurate classification of an acute VTE as either provoked or unprovoked is important clinically because there is mounting evidence that the risk of recurrent venous thromboembolism after 3 to 6 months of anticoagulant therapy is ≈50% lower among patients who have a transient provoking risk factor than among patients who have an unprovoked VTE.4 Although the initial treatment is identical for patients with either an unprovoked or a provoked acute VTE, the clinician must ultimately decide if the patient should remain on indefinite oral anticoagulant therapy, and the answer to this question depends largely, but not entirely, on whether the VTE event is classified as provoked or unprovoked.5–7

Is it ever clear that a patient has a truly unprovoked VTE? It is certainly reasonable to hypothesize that all VTE events are triggered by some transient risk factor.8 The scenario of a 26-year-old patient who develops acute proximal deep vein thrombosis in a leg out of the blue may sound like a straightforward case of an unprovoked clot, but what if this patient had recently taken a short 2-hour airplane flight or reported being sick with an upper respiratory tract infection that required antibiotic therapy 2 weeks before being diagnosed with the VTE? Are these historical findings sufficient to classify the VTE event as being provoked? Unfortunately, there are no clear guidelines that aid the clinician in making this kind of decision.

In light of this important challenge of identifying the presence or absence of a provoking risk factor for VTE, Rogers and colleagues9 report the findings of a study that was designed specifically to do just this, to identify transient or triggering provoking risk factors for acute VTE. The authors used a methodology that is not commonly used to identify risk factors for VTE, namely a case-crossover design.10–12 This study design uses as a case a patient who develops acute VTE during a specified time period (eg, the previous 90 days) and uses as a matched control case the same patient during earlier time periods of equal duration. After a large cohort of patients with acute VTE is assembled, the incidence rate of exposure to potential triggering risk factors is calculated for the time period immediately before the VTE event and compared with the incidence rates in preceding control periods. An example is long-distance air travel. If a large study finds that the frequency of preceding long-haul plane flights is significantly higher in the time period immediately preceding the acute VTE event compared with prior time periods, there would be a statistical association.

This case-crossover design works best if the risk factor being analyzed occurs rarely or intermittently (eg, surgery or air travel), if the effect on VTE risk develops rapidly but is transient (eg, leg injury), and if the outcome (VTE) develops quickly with little time delay. The term crossover is used because, like a classic crossover study analyzing a treatment, the patient serves as his/her own control. Compared with case-control studies, in which controlling for confounding risk factors is often difficult, case-crossover studies use the patient as his/her own control, eliminating the need to control for these risk factors (eg, body weight or body mass index, chronic comorbidity, physical activity, ethnicity, presence of a thrombophilic condition, etc). In the Rogers study, each VTE case contributed 4 similar 90-day control time periods. The authors analyzed ≈400 subjects diagnosed with acute VTE who participated in a prospec-
tive cohort study and had fee-for-service Medicare coverage, which allowed them to link together several administrative databases. Thus, the findings apply primarily to individuals >65 years of age. The potential transient or triggering risk factors that were considered included injectable medications such as erythropoietin-like drugs, chemotherapeutic drugs, and antipsychotic drugs, as well as specific events, such as a leg fracture, other injuries, surgery, infections (defined with specific International Classification of Disease, ninth revision, clinical modification codes), immobility (medical hospitalization), blood transfusion, amputation, and presence of a central venous catheter.

The authors report that the most common triggering event was an infection, which occurred in about half of the cases in the 90 days preceding the diagnosis of VTE and in ~25% of control periods, with a risk ratio of 2.9 after adjustment for exposure to all of the other potentially triggering exposures in a multivariable model. Other significant independent triggers included, as expected, major surgery, fractures, medical hospitalization, and use of chemotherapy. The most interesting triggers were use of erythropoiesis-stimulating agents, blood transfusion, and acute infections. When Rogers et al. restricted their analysis to only patients with cancer, they found that infection, blood transfusion, and insertion of a central venous catheter were significantly associated with the development of acute VTE. These findings are interesting because in the cancer thrombosis literature the principal determinants of acute VTE are thought to be the type of cancer, stage of the cancer, use of chemotherapy, and several clinical findings such as weight, thrombocytosis, and white blood cell count. Triggers such as infection or blood transfusion are generally not considered as VTE triggers in outpatients with cancer.

The findings of this study, coupled with findings in other studies in the literature, indicate that an acute infection, particularly a more severe infection that requires hospitalization, should be considered a trigger for acute VTE. The results from this study also provide evidence that suggests that blood transfusion and the use of erythropoiesis-stimulating agents should now be considered possible triggers for acute VTE in noncancer patients. More studies similar to the study by Rogers et al., using more robust data sets suitable for case-crossover methodology, are needed to better elucidate potential triggers for acute VTE. This is particularly important for younger individuals who are currently categorized as having unprovoked VTE. If the long-term incidence of recurrent VTE is lower in the individuals who have an identified trigger, long-term oral anticoagulation may not be necessary.

Disclosures
None.

References

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