Identifying Risk Factors for Venous Thromboembolism

Running title: White, Risk factors for VTE

Richard H. White, MD
University of California, Davis, Sacramento, CA

Address for Correspondence:
Richard H. White, MD
Department of Medicine
University of California, Davis
4150 V Street, Suite 2400, PSSB
Sacramento, CA 95817
Tel: 916-734-7005
Fax: 916-734-2732
Email: rhwhite@ucdavis.edu

Journal Subject Codes: [8] Epidemiology; [173] Deep vein thrombosis

Key words: deep vein thrombosis; Editorials; pulmonary embolism; risk factors; venous
Our understanding of risk-factors associated with the development of venous thromboembolism (VTE) has increased steadily over the past 20 years. In the 1980’s, the development of VTE was conceptualized in the context of Virchow’s classic triad of factors 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. Patients who had a disease or condition that included one of these factors were considered to have a “predisposing” condition, whereas the patients without any of these factors were categorized as having an ‘idiopathic’ venous thrombosis. In the 1980’s, the principal terms used to categorize acute venous thrombotic events were idiopathic and secondary venous thromboembolism.

Gradually the term “unprovoked”, first coined by Kearon, began to be used instead of idiopathic, and “unprovoked” 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 readily identify a provoking risk-factor becomes less certain as the time between the provoking event and onset of acute VTE increases. Is surgery a provoking risk factor when an acute VTE develops 90 days or 120 days after an operation? The best examples of a persisting-provoking VTE risk-factor include active medical diseases, such as cancer, inflammatory bowel disease, and nephrotic-syndrome, and chronic conditions such as immobility and 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 3-6 months of anticoagulant therapy is approximately 50% lower among the patients who have a transient-provoking risk factors than the patients who have an unprovoked VTE. Although the initial treatment is the same 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.

Is it ever clear that a patient has a truly unprovoked VTE? Many patients with idiopathic/unprovoked VTE go many years before first being diagnosed with acute VTE, so it is certainly reasonable to hypothesize that all VTE events are triggered by some transient risk-factor. 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 two-hour airplane flight or reported being sick with the “flu” that required antibiotic therapy 2 weeks before being diagnosed with the VTE? Are these historical findings sufficient to classify the event as a provoked VTE? Unfortunately, there are no clear guidelines that aid the clinician in making this kind of decision.

It is in the light of this important challenge of identifying the presence or absence of a provoking risk-factor for VTE that Rodgers and colleagues report the findings of a study that was specifically designed to do just this, identify transient or “triggering” provoking risk factors for acute VTE. The authors used a methodology that is not commonly employed to identify risk-factors for VTE, namely a case-crossover design. This study design uses as a ‘case’ a patient who developed acute VTE during a specified time period (e.g. prior 90 days), and uses as a matched ‘control case’, the same patient during earlier time periods of equal duration. After assembling a cohort of patients with acute VTE, the incidence rate of exposure to potential
triggering risk-factors is calculated for the time-period immediately before the VTE event and compared to the incidence rates of risk-factor exposure in preceding control periods. An example would be long distance air travel. If the frequency of preceding long-haul plane fights was 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 (e.g. surgery or air travel); if the effect on VTE risk develops rapidly but is transient (e.g. 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. As compared to case-control studies, in which controlling for confounding risk factors is often difficult, case-crossover studies uses the patient as his/her own control, eliminating the need to control for these risk factors (e.g. body weight or body-mass-index, chronic comorbidity, physical activity, ethnicity, presence of a thrombophilic condition etc.) In the Rodgers study, each VTE case contributed 4 similar 90-day ‘control’ time periods. The authors analyzed approximately 300 subjects diagnosed with acute VTE who participated in a prospective cohort study and had fee-for-service Medicare coverage, which allowed them to link together several administrative data-bases. Thus, the findings apply primarily to older individuals over the age of 65. The potential transient or ‘triggering’ risk factors that were considered included injectable medications such as erythropoietin-like drugs, chemotherapeutic drugs, anti-psychotic drugs, and events such as a fracture, other injuries, surgery, infections (defined using specific ICD-9-CM 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 approximately 25% of control periods, with a risk-ratio of 2.9 after adjusting 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 triggers that were most interesting were use of erythropoiesis stimulating agents, blood transfusion and acute infections. When they 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 finding are interesting, because in the cancer-thrombosis literature the principal determinants of acute VTE are felt thought to be the type of cancer, the stage of the cancer, use of chemotherapy, and several clinical findings, such as weight, thrombocytosis and white blood cell count\textsuperscript{12,13}. Triggers such as infection or blood transfusion are generally not considered in outpatients with cancer.

The findings of Rodgers et al certainly add to accumulating epidemiologic data suggesting that infections and blood transfusions are independent risk factors associated with development of acute VTE, which they discuss in some detail\textsuperscript{14}. Infection can lead to activation of the coagulation system, which likely explains the observed higher risk of VTE, but other underlying comorbidities that contribute to the risk of getting an infection likely also contribute. Unanswered questions related about the role of infection in promoting VTE include whether the site of infection important (urinary tract versus lung), if presence of the systemic inflammatory response is the key factor, and if bacteria lead to a higher incidence of VTE (e.g. gram-negative organisms versus staphylococcal species). In their analysis, Rodgers did for an interaction between immobility (hospitalization) and infection. Infection alone was associated with a 3 fold relative risk of being diagnosed with VTE, but infection coupled with a hospitalization was
associated with a 7 fold increase in the risk of developing acute VTE, and this was true among patients who did not have cancer. Again, being hospitalized likely is associated with more risk factors than simply immobilization.

Most of the literature that describes the use of erythropoiesis-stimulating agents and its effect on VTE risk is in patients with cancer\textsuperscript{15}. Less is known about the risk of these agents in non-cancer patient. In their analysis of non-cancer patents, use of erythropoiesis-stimulating agents was not a statistically-significant independent risk factor for VTE, but with a larger sample size with more exposures, it is likely that use of these agents would have been associated with significant 7-fold increase in the risk of VTE. Only 5 of the 294 non-cancer cases had an exposure in the preceding 90 days versus 4 exposures in approximately 1150 control time periods.

Blood transfusion may also stimulate the coagulation cascade in some fashion. Studies in cancer patients have shown that transfusion of blood is associated with a higher incidence of VTE\textsuperscript{16,17}, but few studies have been done in non-cancer patients. In the study by Rodgers, blood transfusion in the non-cancer patients was also associated with an approximately 3 fold higher risk of being diagnosed with acute VTE. Unfortunately, no data was shown regarding whether these subjects were actively bleeding or if there was an underlying medical condition that itself may have explained the higher risk of VTE (e.g. myelodysplastic syndrome, inflammatory bowel disease, lupus erythematosus) Thus, it should be kept in mind that blood transfusion might simply be marker for acute bleeding, presence of pro-thrombotic medical condition or simply a severe acute disease.

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

Conflict of Interest Disclosures: None

References:


Identifying Risk Factors for Venous Thromboembolism
Richard H. White

Circulation. published online April 3, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/03/28/CIRCULATIONAHA.112.102814