

Risk Factors for Venous Thromboembolism

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Risk factors for venous thromboembolism (VTE) are often modifiable and overlap with risk factors for coronary artery disease. Encouraging our patients to adopt a heart-healthy lifestyle by abstaining from cigarettes, maintaining lean weight, limiting red meat intake, and controlling hypertension might lower the risk of pulmonary embolism and deep vein thrombosis (DVT), although a cause-effect relationship has not been firmly established. For hospitalized patients, guidelines have provided evidence-based strategies to identify patients at risk, such as elderly persons and those with cancer, congestive heart failure, or chronic obstructive pulmonary disease or undergoing major surgery. Most should receive pharmacological prophylaxis, which will minimize the risk of VTE. Because approximately 3 of every 4 pulmonary embolism and DVT events occur outside the hospital setting, patients should also be assessed for persistent high-risk of VTE at the time of hospital discharge. (J Am Coll Cardiol 2010;56:1-7) © 2010 by the American College of Cardiology Foundation

In 2008, Steven K. Galson, MD, MPH, issued the Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism (1). The Surgeon General estimates that, in the U.S. alone, 100,000 to 180,000 deaths occur annually because of venous thromboembolism (VTE). VTE and its complications place a substantial burden on the U.S. health care system (2). The sequelae of post-thrombotic syndrome (3) and chronic thromboembolic pulmonary hypertension (4,5) are sources of morbidity, diminished quality of life, and loss in functional status.

There exists an impression that risk factors for deep venous thrombosis (DVT) and pulmonary embolism (PE) are quite different from risk factors for coronary artery disease. In fact, we are learning that VTE is a cardiovascular disease and that the risk factors for arterial and venous thrombosis are similar. Many of the VTE risk factors might be modifiable by adopting a "heart healthy lifestyle." This provides the cardiologist the opportunity to engage patients to help them reduce the risk of arterial thrombosis and possibly of VTE simultaneously.

Nonmodifiable risk factors such as being elderly or having cancer can be readily identified. They provide an early warning to the cardiovascular practitioner that additional preventive measures will be necessary to avoid DVT and PE. Fortunately, well-established prophylaxis is available and based upon carefully performed trials.

For those patients who do suffer VTE, many will ask whether it is safe to discontinue anticoagulation after a certain period of time. The optimal duration of anticoagulation is one of the most vexing issues in VTE management. However, analysis of a patient's risk factors for recurrence might assist in decision-making.

Too often, a review of risk factors centers on the hospitalized patient. However, we must keep in mind that 3 of 4 VTE events occur outside of the hospital setting (6). Furthermore, there is a relationship between VTE that occurs in the community and previous hospital stay. Many acute DVT and PE cases that occur at home can be linked to a hospital stay or surgical procedure within the preceding 90 days (7). Thus, when conceptualizing risk factors for VTE, we should take into account the entire continuum of care.

This review aims to put an end to "silo thinking" about VTE risk factors (Table 1). First, there is much overlap in arterial and venous thrombosis risk factors. Second, proper prophylaxis against VTE during and after hospital stay has the potential to reduce markedly the frequency of VTE.

Registries

Registries provide an excellent starting point when studying risk factors for VTE. The largest registry that enrolled only patients with PE (and excluded patients with DVT alone) is the ICOPER (International Cooperative Pulmonary Embolism Registry) (8). Consecutive patients ($n = 2,454$) were registered from 52 hospitals in 7 countries in Europe and North America. After exclusion of 61 patients in whom PE was first discovered at autopsy, the mortality rate at 3 months was 15%. Risk factors associated with an increased likelihood

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Abbreviations and Acronyms

COPD = chronic obstructive pulmonary disease

DVT = deep vein thrombosis

MI = myocardial infarction

PE = pulmonary embolism

VTE = venous thromboembolism

of death included: age >75 years, cancer, congestive heart failure, and chronic obstructive pulmonary disease (COPD).

The largest registry with both PE and DVT patients is called the RIETE (Registro Informatizado de la Enfermedad Trombo-Embolica venosa) registry. Of 15,520 consecutive patients with acute VTE, 6,264 had symptomatic nonmassive PE, and 248 had symptomatic, massive PE. The

clinical risk factors predicting death included immobilization for neurological disease, age >75 years, and cancer (9).

The Longitudinal Investigation of Thromboembolism Etiology combined 2 cohorts representing different regions of the U.S. The combined sample comprised 21,680 participants. The age-standardized incidence of first-time VTE was 1.92/1,000 person-years. The 28-day case-fatality rate was 11% after a first VTE episode. Of the cases, 48% were idiopathic and unprovoked, meaning that they were not associated with preceding surgery, trauma, immobilization, or cancer. Those with cancer-associated VTE had a higher 28-day case-fatality rate of 25% (10).

Overlap of Venous and Arterial Thrombosis Risk Factors

Prandoni et al. (11) discovered an association between asymptomatic carotid artery atherosclerosis and DVT in a case-control study of unselected patients with DVT who did not have symptomatic atherosclerosis. Among Canadian patients 20 to 39 years of age presenting with unprovoked VTE, the risk of subsequent myocardial infarction (MI) over the ensuing decade was 4-fold higher compared with control subjects (12). In a Danish registry of DVT patients, the relative risk for MI was 1.60, and the relative risk for stroke was 2.19 at 1 year after the initial event (13). In a U.S. cohort of 304 subjects with VTE, 8 events (2.6%) occurred in the setting of MI (10). There seems to be a relationship between markers of inflammation and venous thrombosis, but proving a cause-effect relationship remains elusive (14). The most convincing “bridge” between venous and arterial thrombosis is the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial of 17,802 apparently healthy men and women with elevated C-reactive protein levels. They received rosuvastatin 20 mg or its placebo for a median of 2 years. The rosuvastatin group had a 43% reduction in venous thromboembolic events compared with the control group (15).

To investigate risk factors for PE in women, the all female Nurses’ Health Study cohort was studied. There were 112,822 women 30 to 55 years of age at baseline who were free of cardiovascular disease or cancer. With 16 years

of follow-up, there were 1,619,770 person-years of follow-up. Two hundred eighty new PE cases were reported, including 125 that were idiopathic and unprovoked (16).

Three major risk factors for PE were found: obesity, cigarette smoking, and hypertension. Women with a body mass index ≥ 29 kg/m² had a relative risk of 2.9 for suffering idiopathic PE. The relative risk of idiopathic PE was 1.9 for women currently smoking 25 to 34 cigarettes/day and 3.3 for women smoking 35 or more cigarettes daily compared with never smokers. Hypertension had a relative risk of 1.9 for idiopathic PE. Data were similar for provoked PE associated with preceding surgery, trauma, cancer, or immobilization.

Obesity was a risk factor for VTE in a case control study in the Netherlands (17) and in a cohort study from the U.S. National Hospital Discharge Survey (18). In the American study, obese women had a greater relative risk for DVT than obese men, 2.75 versus 2.02.

Nutritional factors have received only scant attention as risk factors for VTE. In a prospective study of 14,962 adults over 12 years, 197 noncancer-related VTEs were identified (19). A food frequency questionnaire assessed dietary intake at baseline and at year 6. Eating fish at least once weekly was associated with a 30% reduction in VTE incidence. The top quintile of red meat eaters was twice as likely as the bottom quintile to develop VTE. Those who ate an average of ≥ 2.5 servings/day of fruits and vegetables could lower their VTE risk by at least 30%. Consumption of at least 4 servings of fruit and vegetables daily and at least 1 serving of fish weekly was associated with the lowest incidence of VTE.

Stress has been linked to coronary heart disease but has rarely been studied with respect to VTE risk. In a cohort of 6,958 Swedish men with persistent stress followed for up to 28 years and assessed by questionnaire, two-thirds had a higher rate of PE compared with men who had low stress levels (20). Thus, psychosocial stress might precipitate PE.

Agno et al. (21) performed a meta-analysis of 63,552 patients from 21 case-control and cohort studies to assess the association between cardiovascular risk factors and VTE. Compared with control subjects, the odds ratio for VTE risk was: 2.3 for obesity, 1.5 for hypertension, 1.4 for diabetes mellitus, and 1.2 for hypercholesterolemia.

The association between classic coronary heart disease risk factors and VTE risk factors provides a starting point for individual screening, risk factor modification, and pre-

Table 1 Altering Silo Thinking About VTE Risk Factors

1. VTE and arterial thrombosis risk factors are similar. Counseling patients to modify risk factors might reduce the likelihood of both VTE and myocardial infarction.
2. VTE risk factors persist at home and in skilled nursing facilities. When discharging a patient from the hospital, consider ordering prophylactic measures that continue after hospital discharge.

VTE = venous thromboembolism.

vention. Practitioners can counsel patients with the aim of reducing the frequency of both MI and VTE (Table 2).

Risk Factors Among Hospitalized Patients

Multiple scoring systems are available to identify hospitalized patients at high risk for VTE. Those patients at moderate or high risk warrant prophylaxis, usually with low, fixed preventive doses of anticoagulant drugs such as low molecular weight heparin, unfractionated heparin, or fondaparinux.

The high death rate from PE, which exceeds the death rate from acute MI, emphasizes the need for improved preventive efforts. Failure to institute prophylaxis among hospitalized patients is a much bigger problem with Medical Service patients than Surgical Service patients. The number of patients at risk in the U.S. annually is staggering: more than 7 million Medical Service and 3 million Surgical Service patients (22).

The eighth edition of the American College of Chest Physicians guidelines (23) declares that “every hospital should develop a formal strategy to prevent VTE.” A VTE prophylaxis is effective and reduces by more than one-half the frequency of PE and DVT (24). Nevertheless, it continues to be underused throughout the world (25).

Electronic alerts to physicians whose patients are at high risk but who are not receiving prophylaxis reduce symptomatic VTE by more than 40% (26) and maintain effectiveness over time (27). “Human” alerts, in which a hospital staff member contacts the responsible physician when a high-risk patient is not receiving prophylaxis, can reduce symptomatic VTE by more than 20% (28). Prophylaxis is also cost-effective (29).

Among patients undergoing major surgery, we found low rates of prophylaxis and high rates of inferior vena cava filter insertion in a prospective registry of 5,451 patients with ultrasound confirmed DVT from 183 hospitals in the U.S. Among surgical patients who developed DVT, some form of prophylaxis had been used in only 44%. Once diagnosed with DVT, 20% of surgical patients received permanent inferior vena cava filters (30).

This same registry found that, among patients initially hospitalized for conditions other than VTE, medical patients received prophylaxis less often than nonmedical patients (25% vs. 54%, respectively; $p < 0.0001$) (31). Underuse of VTE prophylaxis extended to both pharmacological

and mechanical modalities. In addition, medical patients developed PE more often (22%) than nonmedical patients (15%) ($p < 0.0001$).

Hospitalized patients with cancer had twice the incidence of DVT and PE as patients without cancer (32), on the basis of the National Hospital Discharge Survey. The highest incidence of VTE was in patients with pancreatic cancer, 4.1%. In the California Cancer Registry, which was linked to the California Patient Discharge Data Set, the highest incidence of VTE in cancer patients occurred during the first year of follow-up (33). The number of VTE events/100 patient-years was: 20 for metastatic pancreatic cancer, 11 for stomach cancer, 8 for bladder cancer, 6 for uterine and renal cancer, and 5 for lung cancer.

What is less clear is the likelihood of a subsequent cancer diagnosis in a patient with newly diagnosed VTE. In a cohort of 1,852 patients with VTE who were followed for 4 years, 105 (5.7%) were diagnosed with new cancer (24). The risk more than doubled for patients who had presented with idiopathic and unprovoked VTE. The annualized risk for new cancer was 1.3/100 person-years of follow-up.

Congestive heart failure was associated with VTE in the National Hospital Discharge Survey (34). The relative risk for PE in patients with congestive heart failure was 2.1 compared with patients with no congestive heart failure. For DVT, the relative risk was 1.2. In a DVT registry of 5,451 patients with ultrasound confirmed venous thrombosis (35), congestive heart failure patients had higher medical acuity with more comorbid diseases such as stroke and pneumonia, more frequent risk factors such as immobilization, and a lower rate of VTE prophylaxis than patients without congestive heart failure. The risk of VTE is low after uncomplicated MI.

The relationship between acute exacerbations of COPD and the prevalence of PE has been uncertain. Therefore, Rizkallah et al. (36) undertook a meta-analysis. They found that the overall prevalence of PE in this population was 20%, but the prevalence was higher—25%—among hospitalized patients. Thus, the diagnosis of PE should be considered in patients with COPD exacerbations severe enough to warrant hospital stay. Similar results were found in a case series of patients in France with unexplained exacerbations of COPD (37).

A myth abounds that patients with chronic kidney disease are not susceptible to VTE because qualitatively defective platelets provide protection against thrombosis. However, a large retrospective cohort study refutes this premise. Two hundred ninety-eight consecutive patients with nephrotic syndrome were followed for an average of 11 years (38). During the first 6 months of follow-up, the incidence of symptomatic VTE was 9.8%. These patients also had a 6-month incident rate of 5.5% for arterial thromboembolism.

The bottom line is that, among hospitalized patients, certain populations deserve special vigilance, because they are especially susceptible (Table 3). They might already have suffered occult VTE.

Table 2 Potential Modification of VTE Risk Factors

1. Obesity: nutritional counseling, exercise, medication, bariatric surgery
2. Cigarettes: cigarette cessation programs, medication, hypnosis
3. Hypertension: exercise, weight loss, medication
4. Diabetes: exercise, weight loss, medication
5. High cholesterol: exercise, weight loss, medication
6. Nutrition: counseling, education
7. Stress: counseling, medication

Table 3 Hospitalized Patients Especially Susceptible to VTE

Major surgery
Cancer
Congestive heart failure
Chronic obstructive pulmonary disease
Chronic kidney disease, especially nephrotic syndrome

VTE = venous thromboembolism.

Risk Factors for Recurrent VTE

Certain clinical risk factors are associated with recurrent VTE despite anticoagulation (Table 4). A cohort study of 673 patients found that 3.0% of patients suffered recurrence despite anticoagulation and that most (79%) recurrences were fatal. Risk factors for recurrence despite anticoagulation included: immobilization, cancer, or COPD (39). A common clinical problem is deciding whether to prescribe time-limited versus indefinite-duration anticoagulation. When anticoagulation is discontinued, the risk of recurrence is higher among men than women (40,41). Other risk factors for recurrence include elevated body mass index (42) and low levels of high-density lipoprotein cholesterol (43). Patients who initially present with symptomatic PE rather than symptomatic DVT also have a higher risk of recurrence (44). Two laboratory coagulation tests have been proposed for use after discontinuation of anticoagulation to predict possible recurrence: D-dimer (45) and thrombin generation (46). However, there is insufficient experience with these tests to recommend them as part of the decision-making process for prescribing indefinite versus time-limited therapy.

The most recent approach to minimizing recurrent VTE is the proposal of flexible dosing rather than traditional fixed dosing (either time-limited or indefinite-duration). Prandoni et al. (47) carried out a randomized trial of 538 patients with initial DVT. They did serial venous ultrasound examinations to determine whether they could lower the recurrence rate with ultrasonography-guided duration of anticoagulation. In the flexible dosing group, patients with recanalized veins were assigned brief durations of anticoagulation, whereas nonrecanalized patients received prolonged courses of anticoagulation. They found that tailoring the duration of anticoagulation on the basis of ultrasonography reduced the rate of recurrent VTE. For now, however, the evidence favors adhering to current guidelines with fixed, time-limited anticoagulation for provoked VTE and indefinite duration anticoagulation for idiopathic VTE (48).

Genetics and the Thrombophilia Workup

The 2 most common genetic risk factors for VTE are factor V Leiden and the prothrombin gene mutation. The most common acquired (nongenetic) cause is antiphospholipid antibody syndrome. Although the genetic risk factors increase the likelihood of an initial VTE, they have little impact on the risk of recurrent VTE. Heterozygous factor V

Leiden triples the risk of an initial VTE, and homozygous factor V Leiden increases the risk approximately 15- to 20-fold (49). The most important predictor of recurrent VTE after discontinuation of anticoagulation is an initial event that is idiopathic and unprovoked (50,51).

Elucidating genetic predisposition to VTE is a complex task. Among 304 individuals who developed VTE while participating in the Physicians' Health Study, several candidate gene polymorphisms were identified that were independently associated with risk of incident VTE. These candidate genes include polymorphisms that mediate inflammation and metabolize lipids (52). Many additional single-nucleotide polymorphisms associated with VTE have been identified (53,54).

Thrombophilia workups are expensive and usually add little to patient management. In general, I would not change the duration of anticoagulation on the basis of the results of testing. The most frequent exception is the finding of elevations in anticardiolipin antibodies. In patients with high anticardiolipin antibody levels who have suffered a thrombotic event, I would consider indefinite duration anticoagulation. Other aggressive thrombophilias include homozygous factor V Leiden, homozygous prothrombin gene mutation, double heterozygote mutations, protein C, protein S, and antithrombin deficiency. I do believe that thrombophilia workups can often satisfy the curiosity of patients, families, and referring physicians who ask whether there was a special predisposition to thrombosis. I usually order a "mini thrombophilia workup" that is not influenced by concomitant anticoagulation (Table 5). Novel thrombophilia tests are being developed that focus on the genetics and biologic effects of thrombosis (55).

Long-Haul Air Travel

Long-haul air travel is possibly the most common risk factor for VTE that is featured in the popular press. However, it is very rare. At Charles de Gaulle Airport in Paris, the incidence of PE was 4.8 cases/million for those traveling more than 10,000 km, compared with 1.5 cases/million for those traveling <5,000 km (56). An overview of travel-related VTE found a 2.8-fold higher rate of VTE in

Table 4 Risk Factors for Recurrent VTE

While taking anticoagulant drugs
Immobilization
Cancer
Chronic obstructive pulmonary disease
After anticoagulant drugs are discontinued
Male sex
Overweight, obesity
Low high-density lipoprotein cholesterol
Presenting with symptoms of pulmonary embolism (rather than symptoms of DVT)
Lack of recanalization of DVT on venous ultrasound examination

DVT = deep vein thrombosis; VTE = venous thromboembolism.

Table 5 “Mini” Thrombophilia Workup

Factor V Leiden
Prothrombin gene mutation
Anticardiolipin antibodies

travelers than in control subjects. There was a dose-response relationship of 18% higher risk for each 2-hour incremental increase in travel duration (57). The American College of Chest Physicians guidelines recommend for high-risk travelers, such as those with prior VTE, graduated compression stockings or a single prophylactic dose of low molecular weight heparin injected before departure, along with common sense measures applicable to all travelers: avoidance of constrictive clothing, ensuring adequate hydration, and undertaking periodic calf muscle contraction (23).

Community-Acquired VTE

Risk factor evaluation is important outside acute care hospital settings (Table 6). In a community-based study in western France, two-thirds of acute VTE events occurred at home. And the incidence of VTE increased markedly with age (58). In a separate French case-control study of non-hospitalized patients, the most common risk factors for VTE were: a history of prior VTE, venous insufficiency, pregnancy, trauma, frailty, and immobility (59). In Olmsted County, Minnesota, a population-based case-control study found that independent risk factors for VTE included: surgery, trauma, hospital stay or placement in a nursing home, and cancer (60).

Especially intriguing are the data emerging from the Worcester Venous Thromboembolism Study. Three-quarters of VTE patients suffered their event in the outpatient setting. Within the preceding 3 months, 23% had undergone surgery, and 36% had been hospitalized. Among those patients, two-thirds experienced VTE within 1 month of hospital discharge. Major risk factors included cancer and prior VTE (7). More than one-half of VTE events occurred in subjects 65 years of age or older (61). Thus, in Worcester, failure to prophylax during hospital stay was associated with the occurrence of outpatient DVT and PE.

Women’s Health

Pregnancy. In a U.S. nationwide inpatient sample, the VTE rate was 1.72/1,000 deliveries, with 1.1 deaths/100,000. The risk of VTE was 38% higher for women 35 years of age and older and 64% higher for black women. Thrombophilia was the most important risk factor (62). During pregnancy, the risk of VTE begins in the first trimester (63). In a Mayo Clinic study, the highest risk period seemed to be post-partum (64).

Hypercoagulability of pregnancy probably evolved to protect women from hemorrhage at the time of childbirth (65). The most important thrombophilias are: factor V

Leiden, prothrombin gene mutation, anticardiolipin antibody elevation, antithrombin deficiency, and protein C and S deficiencies. However, routine thrombophilia screening is not considered cost-effective (66).

Oral contraceptives. Most oral contraceptives combine an estrogen and a progestin. At least 10 million women in the U.S. and 100 million women worldwide use combination oral contraceptives. The risk of VTE is increased by a factor of 3 to 4 among current users. In addition, the risk seems to double for formulations containing desogestrel or gestodene, known as “third-generation” progestins (67,68). Whether women at high risk of VTE should undergo thrombophilia testing before deciding to take oral contraception is controversial.

Post-menopausal hormone therapy. In the Heart and Estrogen/progestin Replacement Study (69) and in a meta-analysis (70), post-menopausal estrogen replacement was associated with an increased risk of VTE. The magnitude of risk was double to triple the baseline likelihood of VTE. Susceptibility to DVT or PE seemed to be highest during the first year of hormone use.

Pediatrics

Venous thromboembolism in children has received little attention. Most VTE affects the upper extremity and is associated with in-dwelling central venous catheters (71,72). The highest incidence is during the neonatal period, followed by another peak in adolescence. Teenage girls have twice the rate of VTE as teenage boys, probably due to use of oral contraceptives and pregnancy (73).

Conclusions

Our goal is to make VTE a rare disease. Careful attention to risk factors is the key to achieving this objective. Until now, risk factors have focused on hospitalized patients to determine whether they should receive anticoagulant or mechanical prophylaxis. The tendency has been to highlight general surgery, immobilization, congestive heart failure, COPD, and a history of prior VTE.

We should now consider additional lifestyle risk factors that patients and their health care providers can modify. These include “cardiac” risk factors such as cigarette smoking, overweight, metabolic syndrome, hypertension, high red meat consumption, and hyperlipidemia. Risk factor

Table 6 Risk Factors for VTE in the Community

Advancing age
Cancer
Prior VTE
Venous insufficiency
Pregnancy
Trauma
Frailty and immobility

VTE = venous thromboembolism.

modification might reduce the likelihood of DVT or PE. We must also include the community into our risk factor analysis. Many community-acquired VTE events are due to inadequate VTE prophylaxis during a recent prior hospital stay or surgical procedure. This link between hospital stay and community VTE requires that we assess the need for prophylaxis at the time of hospital discharge.

New onset DVT or PE in the community that is not related to recent hospital stay might be due to a modifiable “cardiac” risk factor. Therefore, when we counsel our cardiac patients to stop smoking cigarettes, we can tell them that smoking cessation will lower the risk of MI, lung cancer, and possibly VTE.

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Key Words: PE ■ pulmonary embolism ■ risk factors ■ venous thromboembolism ■ VTE.