Risk Factors for Venous Thromboembolism

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Abstract—Until the 1990s, venous thromboembolism (VTE) was viewed primarily as a complication of hospitalization for major surgery (or associated with the late stage of terminal illness). However, recent trials in patients hospitalized with a wide variety of acute medical illnesses have demonstrated a risk of VTE in medical patients comparable with that seen after major general surgery. In addition, epidemiologic studies have shown that between one quarter and one half of all clinically recognized symptomatic VTEs occur in individuals who are neither hospitalized nor recovering from a major illness. This expanding understanding of the population at risk challenges physicians to carefully examine risk factors for VTE to identify high-risk patients who could benefit from prophylaxis.

Factors sufficient by themselves to prompt physicians to consider VTE prophylaxis include major surgery, multiple trauma, hip fracture, or lower extremity paralysis because of spinal cord injury. Additional risk factors, such as previous VTE, increasing age, cardiac or respiratory failure, prolonged immobility, presence of central venous lines, estrogens, and a wide variety of inherited and acquired hematological conditions contribute to an increased risk for VTE. These predisposing factors are seldom sufficient by themselves to justify the use of prophylaxis. Nevertheless, individual risk factors, or combinations thereof, can have important implications for the type and duration of appropriate prophylaxis and should be carefully reviewed to assess the overall risk of VTE in each patient. (Circulation. 2003;107:I-9–I-16.)

Key Words: thrombus ■ risk factors ■ prevention ■ embolism

VTE consists of 2 related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). This review summarizes the strength of the evidence regarding specific risk factors for VTE and provides a guide for identifying patients who could benefit from VTE prophylaxis. This article also identifies population groups whose apparent risk for VTE is too low to justify preventive treatment.

In 1884, Rudolph Virchow first proposed that thrombosis was the result of at least 1 of 3 underlying etiologic factors: vascular endothelial damage, stasis of blood flow, and hypercoagulability of blood. In the last century, recognition that all VTE risk factors reflect these underlying pathophysiologic processes and that VTE does not usually develop in their absence has increased. In a review of 1231 consecutive patients treated for VTE, 96% had ≥1 recognized risk factor (Table 1).1 Furthermore, there is convincing evidence that risk increases in proportion to the number of predisposing factors (Figure 1).2,3 The majority of clinically recognized instances of VTE are suspected because of typical signs and symptoms in individuals who present to an outpatient clinic or hospital emergency department;1 only one quarter to one half of VTE are diagnosed in patients who are or were recently hospitalized.1,4,5

Risk factors convincingly demonstrated for VTE include increasing age, prolonged immobility, malignancy, major surgery, multiple trauma, prior VTE, and chronic heart failure (Table 2). However, it is important to recognize that the predictive values of these factors are not equal. In assessing whether prophylaxis is indicated, physicians should consider both the strength of individual risk factors and the cumulative weight of all risk factors.

Individual Risk Factors Sufficient to Justify VTE Prophylaxis

Strong risk factors having a sufficiently high odds ratio to justify prophylaxis against VTE are listed in Table 2.

Major General Surgery

The risk of VTE after major general surgery has been extensively documented. Although the term “major general surgery” is imprecise, most investigators apply this term to patients who undergo abdominal or thoracic operations that require general anesthesia lasting ≥30 minutes.6,7

Other types of surgery associated with a high risk of VTE include coronary artery bypass,8–10 surgery for gynecological malignancies,11–13 and major urological surgery.7,14 The risk after neurosurgery is similar,15,16 but intracranial surgery presents a relative contraindication to anticoagulant prophylaxis. However, one study did find that prophylactic enoxaparin is safe after elective neurosurgery.17

The recent dramatic increase in endoscopic alternatives to open surgery has not been accompanied by controlled studies of VTE risk, although adverse changes in hemostasis after laparoscopy have been reported.18 Bergqvist and Lowe con-
cluded, in a recent review, that laparoscopic cholecystectomy is a low-risk procedure such that routine VTE prophylaxis is probably not justified. But the decision regarding prophylaxis for laparoscopy should likely be made in the same manner as for conventional surgery, ie, customized for the particular risk of each patient, taking into account the length of the operation, amount of time bedbound, and comorbid conditions.

Major Orthopedic Surgery

Lower extremity orthopedic operations carry a particularly high risk. Without prophylaxis, approximately half of the patients undergoing elective total hip or knee replacement develop VTE. However, only ~5% of these patients manifest symptoms of VTE. Whereas calf vein thrombi tend to be evenly distributed between the 2 legs in patients recovering from hip replacement, ~90% of proximal thrombi occur on the operated side. Patients undergoing arthroscopic knee surgery are at low to moderate risk, so VTE prophylaxis is optional.

Spinal Cord Injury

The overall incidence of DVT within 3 months of paralytic spinal cord injury is 38%; the corresponding frequency of PE is ~5%. The risk appears greatest during the first 2 weeks after injury, and fatal PE is rare ~3 months after injury. The cause of the decrease in clinically evident PE after 3 months is unknown. However, a number of changes associated with chronic paralysis may be involved, including gradual atrophy of the leg muscles and, in many individuals, the development of small caliber collateral veins around organized old venous thrombi that completely obstruct the major deep leg veins.

Fracture of the Pelvis, Hip, or Long Bones

Studies in patients with traumatic hip fracture were among the first to demonstrate the magnitude of VTE in high-risk patients. The problem was further emphasized in 1959 when the first controlled trial of anticoagulant prophylaxis after hip fracture showed a reduction from 10% to 0% of death because of PE. Patients with fractures of the pelvis or femur are also at high risk. The increased risk after cast immobilization of tibial fractures is particularly well documented, with an

![Figure 1.](http://circ.ahajournals.org/)

**Figure 1.** The proportion of patients with clinically suspected deep vein thrombosis in whom the diagnosis was confirmed by objective testing increases with the number of risk factors. (Data adapted from Wheeler et al. *Arch Surg.* 1982;117:1206–1209.)
Overall VTE rate of 45%, but only one third of those being symptomatic.29

**Multiple Trauma**

The early literature examining the association between multiple trauma and VTE was difficult to interpret because of the diverse nature of the injuries and the occurrence of hip and lower extremity fractures in a large proportion of patients.30,31 Geerts et al found DVT in 47% of trauma patients, including proximal DVT in 12%. A low-risk group could not be identified from risk factor profiles in these patients. Not only was DVT found in 56% of patients with lower limb orthopedic or pelvic injury, but 40% of patients in whom the primary site of injury was the face, chest, or abdomen had DVT as well.32

**Malignancy**

The frequency of VTE increases 2- to 3-fold in patients undergoing surgery for malignant disease compared with those undergoing surgery for nonmalignant conditions. Because malignancy is commonly associated with other risk factors, the direct effect of malignancy on risk is uncertain. Advanced cancers are associated with a high incidence of VTE, especially cancers of the breast, lung, brain, pelvis, rectum, pancreas, and gastrointestinal tract.33,34 Administration of chemotherapy increases risk. For example, patients with newly diagnosed multiple myeloma receiving thalidomide with multiagent chemotherapy have an increased risk of thrombotic events.35-37 In addition, women with breast cancer who undergo chemotherapy in association with surgery have 3 times the risk of DVT compared with women who undergo surgery alone.38 The association between VTE and malignancy is described in detail by Lee and Levine elsewhere in this supplement.

**Myocardial Infarction**

Myocardial infarction (MI) is associated with DVT. The VTE risk of patients hospitalized with acute MI is comparable with that of moderate-risk general surgical patients (∼20% overall and 2% symptomatic).39 A number of risk factors are commonly associated with MI, including age, bed rest, and venous stasis because of congestive heart failure, such that MI itself has not been clearly established as an independent risk factor for VTE.

**Congestive Heart or Respiratory Failure**

Patients with congestive heart or respiratory failure are also at risk of venous thromboembolic complications. In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, 15% of patients with class III or IV heart failure treated with placebo had a confirmed episode of VTE.40 Similarly, 16% of patients with class III or IV heart failure treated with low-dose subcutaneous heparin in the Thromboembolism Prevention in Cardiopulmonary Disease with Enoxaparin (PRINCE) study developed VTE.41 Of note, the most critically ill (eg, intubated) patients were excluded from these studies. In both trials, treatment with fixed-dose low molecular weight heparin significantly reduced the risk of VTE. Data on the epidemiology of VTE and its prevention in critically ill medical patients are very limited. Until better data are available, identification of proven VTE risk factors in individual patients and prevention strategies shown to be effective in related patient groups should guide the routine use of prophylaxis during intensive care.42

**Additional Factors That Increase VTE Risk**

The following risk factors are associated with a lower odds ratio for development of VTE (Table 2) and are seldom sufficient individually to justify antithrombotic prophylaxis. Even so, these factors can have important implications for what type and duration of prophylactic treatment is suitable, and the combination of 2 or more moderate and/or weak risk factors may create sufficient cumulative risk to justify the provision of prophylaxis against VTE.

**Prior VTE**

Patients with a previous episode of VTE are at greatly increased risk for recurrence, particularly when exposed to high-risk conditions (eg, major surgery, prolonged immobility, or serious illness). In an observational study of 1231 consecutive patients with VTE, 19% had at least 1 prior clinically recognized episode.41 In a case–control study, patients with a history of VTE were 8 times more likely to develop a new episode during a subsequent high-risk period compared with patients without a history of DVT or PE.43

**Age**

A number of studies support an association between increasing age and a higher incidence of VTE.2,12,44 Patients >40 years of age are at significantly increased risk compared with younger patients, and risk approximately doubles with each subsequent decade. Thus, stratification of risk by the simple dichotomy of age above or below 40 years fails to account for the significantly higher risk among elderly patients.

VTE is rare in children,45,46 and young patients with venous thrombosis usually have strong predisposing factors, such as multiple trauma, leg fractures, or indwelling central venous lines.47,48 White describes the association between VTE and age in greater detail in another section of this supplement.

**Obesity**

Obesity has long been cited as a risk factor for VTE,49 but a number of studies have found no association with excess weight.50 Studies of morbidly obese individuals suggest that the risk of VTE based on obesity alone is low.51 Overweight individuals, whether defined by weight or body mass index, may be at increased risk, but the association of excess weight with VTE is a weak one.

**Immobility**

Gibbs found that 15% of patients on bed rest for <1 week before death had venous thrombosis at autopsy, whereas the incidence rose to 80% in patients in bed for a longer period.52 The influence of immobility as a risk factor is particularly striking in studies of hemiplegia. On the basis of fibrinogen scanning, Warlow et al found asymptomatic DVT in 60% of...
paralyzed limbs of stroke patients compared with 7% in the nonparalyzed limbs.53 Whereas prolonged bed rest or immobility alone does not provide adequate reason for prescribing prophylactic anticoagulant therapy, prolonged immobility combined with other major risk factors increases the likelihood of VTE.

There has been recent attention in the popular press about the risks of VTE associated with long-duration air travel — the so-called “economy class syndrome.” In a study of 231 subjects without a prior history of thromboembolism who were embarking on flights of >8 hours in duration, those randomized to compression stockings had no evidence of DVT on subsequent duplex ultrasonography. Conversely, 10% of untreated individuals developed asymptomatic DVT.54 Despite these findings, there is general consensus that clinically important VTE after air travel is rare, and that the benefits of providing VTE prophylaxis during long distance flights are doubtful.55 Case reports suggest that most cases of travel-related thrombosis affected people at risk because of previous VTE or other predisposing factors. Thus, until a formal study validates another approach, it makes sense to provide advice to such people regarding hazards and simple precautions, including frequent leg movement and adequate hydration during long flights.56

**Varicose Veins**

The importance of varicose veins as an independent risk factor for VTE is controversial, because assessment of varicose vein severity is subjective, and the number of studies is small. A population-based case-control study by Heit et al found that the risk of VTE associated with varicose veins decreases with age: odds ratios 4.2 at 45 years, 1.9 at 60 years, and 0.9 at 75 years.50 On balance, varicose veins are a weak risk factor for VTE. To our knowledge, no one has tested the hypothesis that VTE risk is reduced after surgical removal of varicose veins.

**Pregnancy and the Puerperium**

Fortunately, the absolute risk of developing clinically important VTE during pregnancy or postpartum is low.57 Despite the low incidence, however, PE is a leading cause of maternal death after childbirth, with ~1 clinically recognized PE per 1,000 births and 1 fatal PE per 100,000 births.58,59 The greatest risk occurs during the postpartum period. Carter et al found that the incidence of DVT was similar for pregnant and nonpregnant women of similar age, but the incidence was 20 times higher during the postpartum period compared with an age-matched cohort of nonpregnant women.60 The risk of VTE in pregnant women is increased by smoking, prior VTE, and inherited thrombophilias.61

**Oral Contraceptives**

As oral estrogen compounds became widely available in the late 1960s, early reports suggested an alarming incidence of VTE in young and otherwise healthy women taking oral estrogen to prevent conception.62 A recent case-control study by Lidegaard concluded that the incidence of VTE in young women is between 1 and 3 per 10,000 per year. Pregnancy increases this risk 5 times, low-dose third-generation oral contraceptives 4 times, and low-dose second-generation oral contraceptives 3 times.63

In women receiving hormone-replacement therapy (HRT), the estrogen dose is generally 20% to 25% of that contained in modern oral contraceptives.64 Despite the much lower biological potency, women taking HRT have a 2- to 4-fold increased risk of idiopathic venous thrombosis compared with women not taking HRT.65–68 In the Heart and Estrogen/Progestin Replacement Study, the relative hazard for VTE in postmenopausal women taking estrogen plus progesterin, the most commonly prescribed hormone preparation in the United States, was 2.7.64 More recently, a hazard ratio of 2.1 for PE in healthy postmenopausal women taking estrogen plus progesterin was estimated using data from the Women’s Health Initiative. Women with a history of VTE who are using HRT are at greater risk of recurrence than those with a similar history but not on hormonal therapy.69

Like women receiving estrogens for contraception or menopause, men receiving estrogen therapy for prostate cancer are also at increased risk for VTE.70

**Antiphospholipid Antibody Syndrome**

The overall prevalence of anticardiolipin antibodies and lupus anticoagulants in the general population has not been established with certainty, but rates of 1% to 5% have been estimated,71 with higher rates among the elderly and those with comorbidities such as cancer, severe atherosclerosis, leg ulcer, or chronic and/or acute infection.72 The thrombotic risk associated with these antibodies, particularly in young, otherwise healthy subjects, is also unclear, but thromboembolism rates of 6% to 8% in otherwise healthy patients with lupus anticoagulant have been reported.73 In a case-control analysis involving participants in the Physicians Health Study, those with anticardiolipin antibody titers above the 95th percentile had a 5.3-fold increased risk of developing DVT or PE over a 5-year period.74 Prior thrombosis, a lupus anticoagulant, and elevation of the IgG idiotype anticardiolipin antibodies have all been suggested to increase the risk of thrombosis.75

**Hereditary VTE Risk Factors**

In addition to acquired risk factors, a variety of inherited traits contribute to the overall risk of VTE in a patient (Table 3).76 Antithrombin (AT, previously referred to as AT-III) deficiency was first described in 1965.77 It was not until the 1980s, with the identification of protein C78 and protein S79 deficiencies, that other causes of inherited thrombophilia were recognized. Despite their importance, these entities together account for <10% of all cases of recurrent venous thrombosis. Renewed interest in inherited causes of thrombophilia was sparked by the discovery of activated protein C (APC) resistance by Dahlback et al in 199380 and the prothrombin G20210A mutation by Poort et al in 1996.81 Thus, in >50% of patients with juvenile or idiopathic thrombosis, an inherited thrombophilic condition can now be identified.

**Antithrombin Deficiency**

In unselected patients with VTE, the frequency of AT deficiency is 1.1%,62 compared with 2.4% (range 0.5–4.9%)
in selected patients (Table 3). In general, patients with inherited AT deficiency are at greater risk for VTE than those with protein C or protein S deficiency. In one study, up to 85% of patients with antithrombin deficiency experienced a thromboembolic event by age 50.

**Protein C and Protein S Deficiencies**
The prevalence of heterozygous protein C or protein S deficiency is low in the general population, but 5% to 10% among selected patients with VTE (Table 3). Defects in this natural anticoagulant system greatly increase the risk of thrombosis: As many as 50% of heterozygotes up to 50 years old suffer a thrombotic event.

**APC Resistance**
Between 20% and 60% of patients with recurrent VTE display APC resistance on laboratory testing. In the majority of cases, this is because of a mutation in the factor V gene, labeled factor V Leiden. Among the European white population, the factor V Leiden mutation is the most prevalent hereditary thrombophilia. Approximately 4% to 6% of the general population are heterozygous for this trait (which is autosomal dominant), but it is extremely uncommon among native populations of Africa, Southeast Asia, and Australia.

Although APC resistance is not considered as strong a risk factor for DVT as the previously mentioned thrombophilias, it is still associated with a 3- to 7-fold increased risk of venous thrombosis (Table 3). In addition, the factor V Leiden mutation can greatly enhance the thrombotic risk from other factors. In a study of patients ≥70 years with at least 1 prior episode of venous thrombosis, 11% had the mutation. Up to 60% of women who experience VTE during oral contraceptive use are APC resistant. Finally, coinheritance of factor V Leiden with other heritable thrombophilias has been shown to greatly increase future thrombotic risk.

**Factor II (Prothrombin) G20210A**
As with factor V Leiden, the prevalence of the prothrombin G20210A mutation is highest in white individuals of European descent, ranging from 1.7% to 3%. Data from 1 analysis that included patients from the Leiden Thrombophilia Study found 18% of selected patients (with a personal and family history of venous thrombosis) and 6.2% of unselected patients with VTE were heterozygous for this mutation. The relative risk for thrombosis associated with the 20210A allele was 2.8 (95% confidence interval, 1.4–5.6).

### Table 3. Frequency (%) of Inherited Thrombophilic Syndromes in the General Population and in Patients With Venous Thrombosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>General Population</th>
<th>Unselected Patients With Venous Thrombosis</th>
<th>Selected Patients With Venous Thrombosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT deficiency</td>
<td>0.02–0.17</td>
<td>1.1</td>
<td>0.5–4.9</td>
</tr>
<tr>
<td>PC deficiency</td>
<td>0.14–0.5</td>
<td>3.2</td>
<td>1.4–8.6</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>—</td>
<td>2.2</td>
<td>1.4–7.5</td>
</tr>
<tr>
<td>APC resistance</td>
<td>3.6–6.0</td>
<td>21.0</td>
<td>10–64</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>1.7–3.0</td>
<td>6.2</td>
<td>18</td>
</tr>
</tbody>
</table>

*Age 45 years and/or recurrent thrombosis. Adapted from De Stefano V, Finazzi G, Mannucci PM.*

### Coagulation Factors
Elevated levels of several coagulation factors, including factors VIII, IX, and XI, have been linked with increased thrombotic risk. In the Leiden Thrombophilia Study, 25% of patients with a first episode of VTE had factor VIII levels >150% of normal compared with only 11% of healthy controls. Plasma levels of >150 IU/dL were associated with almost 5 times the risk for an initial event. These findings have been confirmed in several other small studies. Furthermore, patients with prior VTE and elevated factor VIII levels are at significantly increased risk of recurrent VTE.

Elevations in plasma levels of factors IX and XI also appear to modestly increase thrombotic risk. After excluding subjects with other known thrombophilic disorders, patients with factor IX and XI levels above the 90th percentile in the Leiden Thrombophilia Study had a 2.5-fold and 2.2-fold adjusted risk, respectively, for venous thrombosis compared with those with lower values. As with factor VIII, the molecular basis for elevated factor IX and XI levels is unknown, although a genetic component seems likely.

Further information is needed to define the impact of these conditions on future management of VTE, including duration of therapy, prophylaxis in high-risk clinical situations, and family screening. Accordingly, the utility of screening for elevations in these factor levels in patients with idiopathic venous thrombosis remains unclear.

### Hyperhomocysteinemia
The risk of VTE that is directly attributable to hyperhomocysteinemia is unknown. During the past decade, epidemiologic studies have identified mild to moderate homocysteinemia as an independent risk factor for VTE. Among 269 patients with first DVT enrolled in the Leiden Thrombophilia Study, 10% had homocysteine levels above the 95th percentile (adjusted odds ratio for VTE 2.5, compared with healthy matched controls). The same odds ratio was found in a meta-analysis of 10 case–control studies. Patients with elevated homocysteine are also at increased risk for recurrent VTE.

### Other Hereditary Risk Factors
The incidence of VTE in black populations appears higher than in white populations, and both have higher incidences than East Asian populations. Furthermore, men may have a higher incidence of VTE than women. The associations among VTE, race, and sex are weak, however, and do not appear on most lists of clinically important risk factors. White describes this topic in greater detail in another section of this supplement.
Use of VTE Risk Factors to Select Patients for Prophylaxis

In considering VTE prophylaxis, the physician should take into account absolute and relative risks of VTE, potential benefits of available prophylactic agents, possible complications (including the risk of bleeding), and expense. A number of consensus meetings have convened to publish evidence into practical tools for clinical decision-making. In 1986, the American College of Chest Physicians published consensus guidelines for prevention of VTE. These guidelines, updated every 2 to 3 years, have been widely adopted by physicians and hospitals. Every hospital should develop a formal strategy that addresses the prevention of VTE. This should generally be in the form of a written prophylaxis policy, especially for high-risk groups. A computerized order entry system and preprinted or computerized admission orders can be helpful in implementing a strategy for preventive treatment.

There is sufficient evidence to recommend routine prophylactic treatment for several groups of hospitalized patients. These include patients undergoing major general, urologic, and gynecologic surgery; neurosurgery; hip fracture repair; and lower extremity arthroplasty. Those patients admitted with major trauma or spinal cord injury should also receive VTE prophylaxis. All patients admitted to intensive care units should be assessed for VTE risk. Preventive VTE treatment should be given, after careful evaluation, to most patients with acute MI, cancer (particularly those receiving chemotherapy), heart or respiratory failure, ischemic stroke, or severe lung disease.

Highly safe and effective types of VTE prophylaxis include low molecular weight heparin, warfarin, intermittent pneumatic compression, and low-dose unfractionated heparin. Even among proven methods of prophylaxis, important differences in safety and efficacy must be taken into account for different patient groups (eg, those undergoing neurosurgery). Patients with a high risk of bleeding should be started on mechanical methods of prophylaxis (intermittent pneumatic compression and/or elastic stockings) at least until bleeding risk is reduced.

In general, patients with one of the weak or moderate risk factors listed in Table 2 do not require prophylaxis. On the other hand, most patients with multiple factors should be given prophylactic treatment unless specific contraindications exist. A detailed review of specific types, doses, and durations of prophylactic treatments recommended for each population are provided in the most recent (2001) American College of Chest Physicians guidelines, which are scheduled for revision in early 2004.

Duration of VTE Risk

Decreasing lengths of acute hospitalization, particularly in the United States, have prompted questions about whether the risk of VTE is decreasing because of shorter periods of bed rest in hospital patients. On the other hand, it has been suggested that patients sent home earlier after surgery may harbor continuing major risk factors, shifting a proportion of VTE from the hospital to the outpatient setting, where it is difficult to provide prophylaxis and where VTE may go undetected.

Whereas VTE prophylaxis has generally been recommended for 7 to 10 days, recent studies have found that extending preventive treatment through the 4 weeks after hospital discharge is beneficial in patients undergoing surgery for cancer or total hip replacement. Additional data are needed to define the optimal duration of VTE prophylaxis in other high-risk.

Conclusion

Although PE is the most common preventable cause of death among hospital patients in the United States, VTE is often overlooked as a major public health problem and viewed as a complication of hospitalization for another illness rather than as a specific disease entity. The potential public health benefit of preventing VTE is substantial: Data from randomized trials involving general surgical patients suggest that adequate prophylaxis in high-risk patients can prevent VTE in 1 of 10 patients and save the life of 1 of 200 patients. Allocation of additional resources to VTE prevention in high-risk patients is justified by cost–benefit analysis, assuming physicians can identify patients at increased risk and prescribe an appropriate strategy according to individualized risk assessment.

References


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