ABSTRACT
This review addresses the numerous factors that predispose individuals for venous thromboembolic events (VTE). Both acquired and genetically inherited factors are reviewed with their approximate relative risk of developing VTE. Oral contraceptive use and hormone replacement therapy, as well as the prevalence of VTE associated with pregnancy, are also addressed. Particular attention is directed to the frequency of more than 1 predisposing factor being present, further increasing the risk of VTE or its recurrence.

INTRODUCTION
Thromboembolic events are serious, common maladies in medicine affecting persons of all ages. Their etiology encompasses a wide variety of pathology and frequently leads to hospitalization with serious consequences requiring prompt therapeutic intervention. Acute myocardial infarction and stroke caused by compromised arterial flow resulting in ischemia make up the majority of these thromboembolic events. However, VTEs continue to increase in incidence and have posed formidable treatment issues for clinicians involved in their management. VTE accounts for more than 250,000 hospital admissions and between 50,000 and 200,000 deaths annually in this country. More than 60% of patients experiencing their first episode of VTE will require hospitalization, and approximately one-third of cases will be admitted with recurrences, most commonly a deep venous thrombosis (DVT) in the lower extremities.1 Both acute and chronic sequelae of DVT, i.e., pulmonary emboli and post-phlebitic syndrome, respectively, require intervention with anticoagulants, long-term follow-up, and further investigation of factors contributing to the thromboembolic event.2,3

Mechanisms that lead to or predispose individuals to VTEs are many and can be divided into 2 major categories: those due to a genetically inherited mutation of a gene(s) involved in coagulation (Table 1), and those that are acquired as a direct or indirect result of trauma, systemic illness (acute or chronic), or an altered physiologic state, e.g., pregnancy, high altitude, surgery, trauma, malignancy, immobility, etc. Prior to the past decade, providing a definitive genetic etiology for recurrent episodes of VTE was possible in less than 15% of patients. Currently, with the rapid progress in molecular genetics and newer, more accurate in vitro testing, a genetically inherited mutation can now be found in greater than 30% of individuals presenting with VTEs. This improvement can be attributed largely to 2 recently discovered mutations of genes involved in clotting: factor V Leiden and prothrombin gene 20210G/A mutation, both having been recognized with significant frequency in individuals presenting with VTE and in the unaffected general population. Given the interest generated by these recent discoveries and their clinical implications, it is likely that other important mutations involving the clotting system will be forthcoming, further contributing to our knowledge of this pervasive clinical problem.

GENETICALLY INHERITED HYPERCOAGULABLE STATES
The earliest discoveries of genetic defects linked to venous thrombosis were the abnormalities of the genes encoding for antithrombin III, protein C, and protein S.4-6 Although these genetic defects are rare (found in less than 1% of the population), their presence has been associated with a high risk of VTE, estimated to be greater than 10-fold.7 Genetic testing for these defects, although more complicated and less reliable, should be part of screening in thrombophilic patients, along with a thorough family history.

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Factor V Leiden
This genetically inherited mutation was discovered in 1993 by Dahlback et al as a result of the studies done in Sweden on patients with thromboembolic disease who characteristically had a poor anticoagulant response to activated protein C. It is currently recognized as the most common genetic defect associated with thrombophilia.8 Subsequent studies have shown that this mutation is present in 4%-6% of the general population and is associated with a 6-fold increased risk of VTE in heterozygote individuals, while homozygotic affected persons have an estimated 80-fold increased risk.9-13 It was found to be present in 15%-20% of patients presenting with their initial VTE, but the risks of recurrent DVT are similar among carriers of the factor V Leiden gene to those without this mutation. Its prevalence appears to be higher in Caucasians, found in 4.4% in the general population of northern Europe and 3% in North America, and is less common in African Americans.14-16 The genetic defect is represented by a substitution of glutamine for valine at the 506 position, rendering the factor V molecule resistant to degradation by activated protein C. Two other mutations of factor V have since been discovered (factor V Cambridge and factor V Hong Kong) that are also associated with factor V resistance to activated protein C, but neither have been associated with the same degree of thrombophilia as factor V Leiden.17,18

Prothrombin G 20210A Gene Mutation
(Prothrombin 20210 G/A)
In 1996 Poort et al reported a gene mutation associated with elevated levels of plasma prothrombin. The mutation occurs at the 20210 position in the 3’ untranslated region of the prothrombin gene where a glutamine is substituted for an arginine, and is currently recognized as the second most common genetic abnormality associated with an increased risk of VTE.19 It is believed to be present in up to 3% of the United States’ Caucasian population,20-22 and its prevalence in the general population of the Netherlands is reported to be 1.2%. Heterozygous individuals have a 3-fold risk of developing VTE. The diagnosis should be suspected when the plasma prothrombin levels and activity are increased when accompanying a VTE event. It should also be kept in mind that individuals who have this mutation may also be positive for factor V Leiden.19 The presence of both factor V Leiden and prothrombin 20210G/A mutation will further increase the risk of VTE and also the risk of recurrent VTE.23,24

Hyperhomocysteinemia
Elevated plasma homocysteine levels (>15 mmol/L) have been found to be an independent risk factor for vascular disease and linked to early occurrence of atherosclerosis, and should be suspected in patients with coronary artery disease, carotid atherosclerosis, and stroke occurring at a young age. However, thrombosis can occur on the venous side of systemic circulation, as well as the arterial. Hyperhomocysteinemia can be due to either a mutation of the gene that encodes for methylenetetrahydrofolate reductase or acquired as a result of poor nutrition, i.e., diet deficient in folic acid, vitamin B12 or vitamin B6.25-27 Several mechanisms have been proposed for the thrombophilic state induced by the elevated plasma levels of homocysteine: oxidative damage to the endothelium that results in inhibition of thrombomodulin on the surface membrane which, in turn, decreases protein C activation and increases the activity of factors XII and V.28 Increasing folic acid intake alone, as well as combining folic acid with vitamin B12 or vitamin B6, will promptly lower the plasma homocysteine level in both the genetically inherited and the acquired forms of the deficiency. However, the effect of these supplements on the incidence of vascular disease has yet to be determined.

ACQUIRED CAUSES OF THROMBOPHILIA
Lupus Anticoagulants and Antiphospholipid Antibody Syndrome (LA/APS)
LA/APS has been associated with both arterial and venous thrombosis and an increased risk of recurrent VTE compared to patients who test negative or are without this syndrome.29,30 It is found in approxi-
mately 20% of patients presenting with VTE and in about 10% of patients presenting with their first ischemic stroke.\textsuperscript{31-33} LA/APS represents a plasma inhibitor and its prevalence in the general population is not known. This inhibitor is usually an IgG antibody that targets the phospholipid substrate of the prothrombin complex portion of the clotting mechanism. LA/APS can occur in patients of all ages and is most commonly diagnosed by abnormal coagulation tests, usually a prolonged partial thromboplastin time (PTT) that does not correct with the addition of normal citrated plasma, but corrects with the addition of a phospholipid substrate to the patient’s plasma. Although it has been associated with autoimmune diseases, its etiology in the majority of cases is unknown and its presence has been associated in 5% to 15% of women having a history of recurrent spontaneous abortions.\textsuperscript{34-36}

An unexplained prolonged PTT usually raises the suspicion of a possible inhibitor and provides the incentive to pursue further laboratory testing. A prolonged diluted Russell venom viper time (dRVVT) will further raise suspicion of the presence of LA. Further testing by using a phospholipid substrate added to the patient’s plasma will remove the inhibitor, confirming the presence of LA. The PTT-LA is another laboratory test that uses a hexagonal phase phospholipid (phosphatidylethanolamine) added to the patient’s plasma that is then mixed with an LA-sensitive reagent to determine the presence of a plasma inhibitor.\textsuperscript{37,38} Antiphospholipid antibodies are frequently absent in patients when the dRVVT and PTT-LA are positive. A variety of methods have been employed to measure their titer, but their presence is less sensitive and predictive of a VTE event. The presence of antibodies by enzyme immunoassay to \( \beta_2 \)-glycoprotein I, when expressed by its binding to phospholipid, may serve as a more sensitive means of predicting VTE.\textsuperscript{39} The pathogenesis of thrombosis in patients with LA/APS is unknown, although a number of mechanisms have been proposed, including inhibition of endogenous anticoagulants, such as thrombomodulin, protein C, antithrombin III, or prostacyclin.\textsuperscript{40-43} However, it is likely that multiple factors and mechanisms contribute to this phenomenon, increasing the risk for VTE.

In a review by Love and Santoro on the prevalence and clinical significance of LA and antiphospholipid antibodies in various populations of patients at risk, patients were divided into those with systemic lupus erythematosus (SLE), other autoimmune diseases, and those without. Multiple series reports were analyzed. The prevalence for positive LA in patients with SLE or an autoimmune disease was 34% and 44% for antiphospholipid antibodies. The prevalence of LA in the general population has been estimated to be 2% and 7.5% for antiphospholipid antibodies.\textsuperscript{44} The increased risk of thromboembolic events associated with these prothrombotic factors was difficult to assess, in large part because of the frequency of other underlying disease or conditions that may have contributed to the risk of VTE.

\textbf{Infection and Inflammation}

The clinical setting of acute and chronic infection, as well as chronic inflammatory diseases, has been associated with some degree of endothelial cell damage resulting from a complex network of inflammatory mediator substances and cytokines (e.g., ser. amyloid A, interleukins, C-reactive protein, tumor necrosis factor-\( \alpha \), and endotoxins) capable of activating the clotting mechanism, inducing a hypercoagulable state.\textsuperscript{45-47} In addition, levels of certain clotting factors believed to increase the risk of DVT, i.e., factor VIII and fibrinogen, as well as autoantibodies, are reported to be elevated in rheumatoid arthritis, inflammatory bowel disease, Kawasaki disease, and SLE, and may be contributing factors to the increased incidence of VTE linked to these illnesses.\textsuperscript{48-50}

\textbf{Malignancies}

It has been long appreciated that malignancies are associated with an increased incidence of VTE and are a common complication of advanced stage cancers, perhaps due to the procoagulant substances elaborated by the tumor. Although the risks vary with the different types of cancer, higher risks have been found in a variety of adenocarcinomas, e.g., pancreatic, ovarian and breast, as well as tumors of the brain.\textsuperscript{51-53} Hematologic malignancies, especially myeloproliferative diseases, are frequently complicated by VTEs occurring in the large visceral vessels, i.e., mesenteric, portal, and hepatic veins, as well as the deep veins of the lower extremities. Not infrequently, a VTE may be the presenting clinical sign of an occult malignancy.\textsuperscript{54-56} Thus, in addition to the usual screening studies recommended in patients presenting with VTE without obvious cause or predisposing factors, one should consider the possibility of an occult malignancy as a cause of hypercoagulability. A complete chemistry panel, imaging studies (computed tomography), and a bone marrow biopsy can be of assistance in ruling out this possibility.

\textbf{Surgery and the Risk of VTE}

Surgical intervention, whether elective or emergent, has
been associated with an increased risk of VTE. This risk is especially high during the first 2 weeks following surgery, but has been reported as late as 5 weeks post surgery.57,58 Orthopedic and neurosurgical procedures have the highest incidence of VTE and pulmonary emboli, and although these risks have been mitigated to a significant degree by the routine use of prophylactic anticoagulants, the risk remains high, with a DVT incidence of 20% to 30% in patients undergoing hip or knee replacement surgery.59-62 Additionally, reports of fatal pulmonary emboli have been reported in 3% to 6% of patients following hip replacement surgery and 13% of those with traumatic hip fractures.63 The risk of VTE in neurosurgical patients remains high and has been reported as occurring in 20% to 50% of patients not receiving prophylactic anticoagulant therapy and a 1.5% to 5% incidence of fatal pulmonary emboli, providing a compelling need for thromboprophylaxis.64-67 The risk will be even higher in these patients if a concurrent illness, malignancy, or predisposing genetic mutation is present at the time of surgery.

Another high-risk group for VTE are those patients who have sustained major trauma, with an incidence of 50% to 60% being reported with traumatic fractures and head injuries.68,69 This risk will be increased further by the surgical intervention that is frequently necessary in these situations, and anticoagulation therapy must be carefully considered because of the risk of major bleeding.

Oral Contraceptives and Hormone Replacement Therapy
Numerous studies have provided convincing evidence of an increased risk of VTE in women using oral contraceptives and, although the amount of estrogen in the newer forms of these agents has been significantly reduced (100 mg to 30 mg of estradiol), no convincing data exist that the incidence and relative risk of VTE have been decreased. Newer progestosterone-containing oral contraceptives have been reported to have a 2-fold risk of VTE. However, it appears that there is a significantly lower risk when progesterone alone is used for contraception.70-74 The risk for users of agents not combined with progesterone ranges from 4- to 8-fold with the generally accepted risk being 4% to 5%.75,76 Women on oral contraceptives who are heterozygous for factor V Leiden or prothrombin 20210G/A mutation have a greatly increased risk for VTE, with 20- to 35-fold increased risk for those positive for factor V Leiden.77-79 Therefore, in this population of patients using oral contraceptives, it is important to consider other factors that have an impact on the risk of VTE, i.e., an occult or known genetic or acquired independent risk factor that may act synergistically with oral contraceptive use, further increasing the risk of VTEs.

Estrogen preparations commonly used for hormone replacement therapy are usually conjugated, as compared to unconjugated preparations used in oral contraceptives, and are associated with a lower risk of VTE in users. However, recent studies have demonstrated a 2- to 4-fold risk of VTE in users of hormone replacement therapy compared to non-users.80-83 The addition of progesterone to these agents has not changed the relative risk, and, unfortunately, there are no large clinical studies to determine the risk associated with the transdermal preparations of hormonal therapy.

Given the prevalence of factor V Leiden, prothrombin 20210G/A gene mutation, and LA in the general population, it raises the issue as to whether women should be screened for predisposing factors before initiating oral contraceptive or hormone replacement therapy. It is clear, however, that a careful family history should be obtained before prescribing oral contraceptives to identify the possibility of existing genetically predisposing factors.84 Current thinking is that there is no need to screen individuals who have a negative family history and no prior episode of VTEs.

Pregnancy and Thrombophilia
Pregnancy has been associated with a 4-fold increase in VTE; the majority occurring during the second and third trimesters, and an even higher risk is reported during the immediate postpartum or puerperal period.85-87 The increased risk has long been attributed to the elevated levels of certain procoagulants present during the later stages of pregnancy, resulting in a heightened state of the clotting system prone to activation by subtle triggering mechanisms often related to the altered physiologic state.88,89 However, recent investigations have revealed a surprisingly high incidence of inherited genetic defects linked to thrombophilia, which may be responsible for the increased incidence of VTE occurring during pregnancy. In a recent study by Martinelli et al, women whose pregnancy was complicated by a VTE were compared for inherited thrombophilic factors against a group who experienced a normal pregnancy.90 The group who had a VTE during pregnancy had a 39.5% incidence of a genetic mutation, increasing their risk of VTE. The group who experienced a normal pregnancy had a 6.5% incidence of an inherited thrombophilic factor (Table 2). Salient points of that study were that the events included a higher incidence of VTE during the second and third trimesters
than during the first, the incidence of VTE was similar for women with thrombophilia during the first pregnancy as during subsequent pregnancies, and finally 43% of the VTEs occurred during the pregnancy, while 57% occurred in the puerperal period.

**Heparin Induced Thrombocytopenia (HIT)**

The association of HIT with an increased risk of a thromboembolic event presents a vexing paradox to the managing clinician who has prescribed prompt anticoagulation therapy with heparin. The thrombocytopenia can frequently be severe, posing the problem of hemorrhage and yet be complicated by both arterial and venous thrombosis. Although the devastating arterial thrombi that occur in the central nervous system or extremities resulting in stroke or acute limb ischemia, respectively, have received much attention, VTEs are more common events related to this syndrome.91-93 The incidence of this complication occurring in patients who develop HIT ranges from 33% to 50% and requires treatment with agents that inhibit thrombin.94

**DISCUSSION**

Individuals in the general population may be at risk for VTEs due to multiple risk factors, both acquired and genetic. Obviously, the acquired risk factors are more common and, when present in combination with a genetically predisposing factor, further enhance or increase the risk of thrombosis. This is particularly relevant when considering the high prevalence of factor V Leiden in the general population and the common use of estrogens (birth control and hormone replacement therapy) by women. In addition, high risk of VTEs has been recognized in those individuals with multiple genetic defects. A particularly common combination of predisposing genetic defects resulting in thrombophilia is the increased incidence of factor V Leiden occurring in patients with prothrombin gene 20210G/A mutation, as was recognized by the studies done at the Leiden Thrombosis Center in The Netherlands.19

It is imperative that individuals who present with their first episode of spontaneous VTE (without a known or apparent triggering mechanism) before age 50 be screened for predisposing factors, and those with a history or recurrent DVT should also be screened. Recommendations for screening thrombophilic patients should include genetic testing for all the commonly known, genetically inherited mutations involving the clotting mechanism and functional assays for antithrombin III, protein C, and protein S. Hematologic assays for the total and free protein S are also important in ruling out deficiency of this factor. In addition, because of its prevalence and relationship to thromboembolic events, coagulation studies should be performed to detect a lupus anticoagulant (dRVVT/phospholipid hexagonal phase-PTT ratio) (Table 3). Antiphospholipid antibodies can be detected with the enzyme-linked immunosorbent assay test method. Results of these studies can assist the clinician in determining the duration and perhaps the type of anticoagulation that should be administered. In addition, genetic testing for family members should be encouraged.

Although not the principal focus of this review, treatment of both the genetically inherited and acquired hypercoagulable states presenting with VTE with anticoagulation therapy is an important, prompt intervention. However, many treatment issues remain controversial. Primary prevention seems reasonable in situations in which patients are deemed at high risk for thromboembolic events, but the timing and level of em-

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**Table 2. Risk of Venous Thromboembolism Associated with Thrombophilia During Pregnancy and Puerperium**

<table>
<thead>
<tr>
<th>Type of Thrombophilia</th>
<th>Women with Thrombosis During Pregnancy or Puerperium (N=119)</th>
<th>Women with Normal Pregnancies (N=232)</th>
<th>Relative Risk (95% CI)</th>
<th>Relative Risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of thrombophilia</td>
<td>47 (39.5%)</td>
<td>15 (6.5%)</td>
<td>9.1 (5.6-14.8)</td>
<td>9.0 (4.7-17.1)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>2 (18.5%)</td>
<td>6 (2.6%)</td>
<td>10.6 (5.6-20.4)</td>
<td>8.7 (3.4-22.5)</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>7 (5.9%)</td>
<td>7 (3.0%)</td>
<td>2.9 (1.0-8.6)</td>
<td>1.8 (0.6-5.4)</td>
</tr>
<tr>
<td>Antithrombin, protein C or protein S deficiency†</td>
<td>9 (7.6%)</td>
<td>2 (0.9%)</td>
<td>13.1 (5.0-34.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Double thrombophilic abnormalities‡</td>
<td>9 (7.6%)</td>
<td>0</td>
<td>∞</td>
<td>∞</td>
</tr>
</tbody>
</table>

CI = confidence interval; NA = not applicable for the small number of positive controls.
* adjusted for parity.
† among cases, 1 antithrombin, 6 protein C, 2 protein S deficiency; among controls, 1 antithrombin and 1 protein S deficiency.
‡ 3 factor V Leiden and prothrombin mutation, 2 factor V Leiden and antithrombin deficiency, 1 prothrombin mutation and protein S deficiency.
The pervasiveness of VTE and the associated complications of this chronic disease present a formidable challenge to the clinician and emphasize the need for recognizing the multitude of predisposing factors. The list of both the more commonly inherited and acquired factors continues to lengthen with newer, more sophisticated testing. Prompt effective therapy can only be rendered when clinical awareness and a high index of suspicion are present. Hopefully, frequent periodic reviews on this subject will contribute to this awareness and expedite appropriate treatment.

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REFERENCES


73. O’Brien PA. The third generation oral contraceptive contro- versy. The evidence shows they are less safe than second generation pills. BMJ. 1999;319:795-796.


92. Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R,


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