Certain individuals may have an abnormal propensity to develop venous or arterial thrombosis and either experience thromboembolic events relatively early in life or suffer recurring events. This well-described clinical phenomenon, paralleled by familial clustering of thrombotic phenotypes, has led to a comprehensive search for inherited and acquired forms of hypercoagulability as part of the condition known as thrombophilia. Although clearly defined associations have been described for hypercoagulable states and thrombosis within the venous system, the establishment of causative or contributing roles for these same thrombophilic conditions and the occurrence of arterial thrombosis has been considerably more elusive.

The World Health Organization/International Society of Thrombosis and Hemostasis in 1995 defined thrombophilia as an unusual tendency toward thrombosis. Frequently cited features traditionally include (1) early age of onset; (2) recurrent episodes; (3) strong family history; (4) unusual, migratory, or widespread locations; and (5) severity out of proportion to any recognized stimulus. Here, we provide an updated review of hypercoagulable states in cardiovascular disease in 3 sections: (1) inherited hypercoagulable states; (2) acquired hypercoagulable states; and (3) diagnosis and management.

Inherited Hypercoagulable States

Establishment of the role of pathways that lead to heritable hypercoagulable phenotypes in multifactorial disorders such as cardiovascular diseases is complicated by the inability to adequately discern the necessity and sufficiency of proposed mediators of hypercoagulability (Figure 1). Hyperhomocysteinemia is a good example of the challenges faced. Elevated homocysteine levels exert numerous vasotoxic effects on the endothelium, which lead to endothelial cell dysfunction, platelet activation, and thrombus formation and an increased risk of thrombotic events. A C677T point mutation within the coding region of the methylenetetrahydrofolate reductase (MTHFR) gene is the most common genetic cause of hyperhomocysteinemia, with homozygotes for the 677T allele exhibiting mild to moderate elevations of serum homocysteine and a varying propensity for symptomatic arterial thrombosis. However, despite studies showing a clear association between the 677TT genotype and hyperhomocysteinemia (gene-intermediate phenotype association), and other studies demonstrating a relationship between hyperhomocysteinemia and arterial thrombosis (intermediate phenotype-disease association), studies attempting to establish a conclusive link between genotype and clinical disease (genotype-disease association) have yielded conflicting results. Additionally, the lowering of plasma homocysteine levels has failed to reduce ischemic events in large randomized trials. It is therefore uncertain whether hyperhomocysteinemia plays a causative role or is merely an epiphenomenon or nonfunctional biomarker among individuals at risk for atherothrombosis and related events. These observations illustrate some of the major challenges in determining the biological and clinical relevance of putative hypercoagulable gene variants.

The difficulty in establishing a clear link between genotype and the risk of multifactorial disease in small case-control studies is frequently the result of limited statistical power, because individual polymorphisms only impart a small overall risk toward clinical events. This may be resolved by pooling multiple smaller studies in a well-designed meta-analysis, as demonstrated in a study of the coronary disease risk conferred by 7 hemostatic polymorphisms. Although numerous smaller studies investigating the association of the factor V Leiden and prothrombin G20210A gene mutations with arterial thrombosis show conflicting results, Ye et al demonstrated in a very large meta-analysis of 66155 cases and 91307 control subjects across multiple heterogeneous populations that these 2 mutations were associated with a modest but significantly increased risk of coronary artery disease and myocardial infarction (MI), with point estimates of 1.17 and 1.31, respectively.

Procoagulant and Fibrinolytic Systems

The complex network of biochemical events regulating mammalian coagulation comprises 5 proteases (factors II, VII, IX, and X and protein C) that interface with 5 cofactors (tissue factor, factor V, factor VIII, thrombomodulin, and surface membrane proteins) to generate fibrin. A delicate balance exists between powerful endogenous procoagulant and thromborestrictant forces to ensure the fluidity of blood.

The direct influence of genetic factors on hemostatic plasma protein concentrations is supported by studies including monozygotic and dizygotic twin pairs. Twin studies present a unique opportunity to study gene-environment interactions.
Pathophysiology of Inherited Hypercoagulable States

Figure 1. Pathophysiology of inherited hypercoagulable states. MTHFR indicates methylenetetrahydrofolate reductase. This figure only depicts inherited hypercoagulable states with well-described associations of genotype with phenotype and of phenotype with clinical disease. Other inherited hypercoagulable states are listed in the Table.

interactions, because monozygotic twins share 100% of their genes, whereas dizygotic twins on average share only 50% of their genome. Genetic model fitting showed that gene coding is responsible for 41% to 75% of the variation in fibrinogen, factor VII, factor VIII, plasminogen activator inhibitor type 1 (PAI-1), factor XIII A and B subunits, and von Willebrand factor (vWF), with a higher monogenic than dizygotic correlation. Similarly, factor XII, factor II (prothrombin), and factor V plasma levels are altered by the presence of the factor XII C46T and factor XII polymorphisms within the factor XII gene, the prothrombin G20210A polymorphism within the factor II gene, and the factor V Leiden polymorphism, respectively.

The correlation between circulating procoagulant factors and the risk of arterial thrombosis was first described in studies reporting the association of elevated concentrations of fibrinogen, factor VII, and vWF with vascular risk and cardiovascular outcomes. Subsequently, elevated levels of tissue factor and factors VIII, IX, XI, and XII were reported as markers of heightened thrombotic risk (Table). More recently, abnormalities in the kallikrein–kinin system have also been shown to increase the risk of arterial events, as seen in the Second Northwick Park Heart Study, which showed that lower levels of inhibitory complexes of the kallikrein–kinin system enzymes, factor XIIa–CI esterase inhibitor, and kallikrein–CI–inhibitor complexes were more common in men who experienced an MI within 10 years of follow-up.

Disorders of the fibrinolytic system have also been linked to an increased risk of arterial thrombosis. Increased levels of PAI-1 and tissue plasminogen activator are found more commonly in patients with acute MI than in control subjects (Table). Similarly, in the Prospective Epidemiological Study of Myocardial Infarction, individuals with tissue factor pathway inhibitor levels below the 10th percentile had a 2.13-fold increased risk of coronary events compared with those with levels above it (95% confidence interval 1.08 to 4.18).

Platelets
Platelets show substantial interindividual variation in activation, aggregation, their surface receptors, and secreted contents, as well as in their interaction with numerous other circulatory components. Given the critical role of platelets in arterial thrombosis, this variability may influence the risk of atherothrombosis.

Heterogeneity of platelet responses to a procoagulant stimulus occurs not only at the interindividual level but also the intraplatelet level. A single population of platelets with increased binding of factor V, factor VIII, factor IX, and factor X in response to thrombin and convulxin (a stimulus for collagen receptor activation) stimulation have been identified. As the percentage of platelets with greater coagulation protein binding increased, factor Xa and thrombin generation increased accordingly. However, despite maximal convulxin concentrations, only half of the platelets identified in the subpopulations increased coagulation protein binding, which indicates intraplatelet heterogeneity.

Several studies have demonstrated the heritability of platelet function within families. The Framingham Heart Study showed that heritable factors were key determinants of the platelet aggregation response, contributing more strongly than environmental covariates to ADP- and epinephrine–induced aggregation and collagen-stimulated lag time. Bray and colleagues established the role of heritability factors in determining platelet response to agonists using extended family structures in white and black subjects with a documented family history of premature coronary artery disease. A separate study in the same population found that heritability
contributed more strongly than clinical covariates to variabil-
ity in the platelet response to aspirin. Moreover, the ability of glycoprotein (GP) Ibα and VI genetic polymorphisms to predict the clinical response to hormone replacement therapy (HRT) of the Heart and Estrogen/Progestin Replacement Study (HERS) is a clear indica-
tion that genetic markers of susceptibility to arterial throm-
botic events have the potential to inform therapeutic decision
making. In a subgroup analysis of HERS, HRT increased the
hazard ratio of coronary events in patients with the GP
Ibα[H9251]-5TT genotype (wild type) by 16% and reduced the
hazard ratio in patients with the TC and CC genotypes by
46%. HRT reduced the hazard ratio in patients with the GPVI
13254TT genotype (wild type) by 17% but increased the
hazard ratio in patients with the TC and CC genotypes by
35%. This study was the first to show a diametrically opposite
therapeutic response with hormone therapy in subjects with
specific polymorphisms in platelet surface glycoproteins
compared with subjects possessing the wild-type genotype,
thus paving the way for future strategies in pharacog-
enomic/personalized medicine.

Platelet-specific polymorphisms in the GP IIIa, GP Ibα,
and GP VI genes have shown an association with an increased
risk of cardiovascular events in some but not all studies
(Table). The large meta-analysis by Ye et al11 did not show
significant overall associations between the GP Ia 807T, GP
Ibα [-5]C, and GP IIIa 1565T gene variants and coronary

---

### Table. Hypercoagulable States

<table>
<thead>
<tr>
<th>Inherited Hypercoagulable States</th>
<th>Association With Arterial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coagulation proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td>CAD,* stroke*</td>
</tr>
<tr>
<td>β-Chain −455 G/A</td>
<td>CAD,* stroke‡</td>
</tr>
<tr>
<td>β-Chain −854 G/A</td>
<td>CAD†</td>
</tr>
<tr>
<td>β-Chain −1420 G/A</td>
<td>CAD‡</td>
</tr>
<tr>
<td>β-Chain C51</td>
<td>CAD†, stroke‡</td>
</tr>
<tr>
<td>C51</td>
<td>CAD‡</td>
</tr>
<tr>
<td>α-Chain Thr312Ala</td>
<td>CAD‡</td>
</tr>
<tr>
<td>Prothrombin G20210A variant</td>
<td>CAD,* stroke,*</td>
</tr>
<tr>
<td>Factor V Leiden (G1691A)</td>
<td>CAD†, stroke*</td>
</tr>
<tr>
<td>Tissue factor antigen level</td>
<td>CAD†</td>
</tr>
<tr>
<td>Tissue factor pathway inhibitor</td>
<td>CAD‡</td>
</tr>
<tr>
<td>Factor VII level</td>
<td>CAD‡</td>
</tr>
<tr>
<td>FXII C46T</td>
<td>CAD‡</td>
</tr>
<tr>
<td>FXIII Val34Leu</td>
<td>CAD‡</td>
</tr>
<tr>
<td>vWF antigen level</td>
<td>CAD†</td>
</tr>
<tr>
<td>vWF Thr789Ala</td>
<td>CAD‡</td>
</tr>
<tr>
<td>vWF Smal polymorphism in intron 2</td>
<td>Stroke‡</td>
</tr>
<tr>
<td>Thrombomodulin antigen level</td>
<td>CAD†</td>
</tr>
<tr>
<td><strong>Fibrinolytic system</strong></td>
<td></td>
</tr>
<tr>
<td>PAI level</td>
<td>Stroke†</td>
</tr>
<tr>
<td>PAI-1 −6754G/5G</td>
<td>CAD*</td>
</tr>
<tr>
<td>Thrombin activatable fibrinolysis inhibitor level</td>
<td>CAD‡</td>
</tr>
<tr>
<td>TAFI Ala147Thr, 1542C/G</td>
<td>CAD‡</td>
</tr>
<tr>
<td>tPA</td>
<td>CAD†, stroke‡</td>
</tr>
<tr>
<td>tPA : Alu insertion/deletion</td>
<td>CAD‡</td>
</tr>
<tr>
<td>tPA −7351C/T</td>
<td>CAD†, stroke‡</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet hyperreactivity</td>
<td>CAD†</td>
</tr>
<tr>
<td>GP Ila Leu33Pro</td>
<td>CAD*</td>
</tr>
<tr>
<td>GP 1Ba −5C/T</td>
<td>CAD†</td>
</tr>
<tr>
<td>GP 1a C807T</td>
<td>CAD‡</td>
</tr>
<tr>
<td>GP 6 T13254C</td>
<td>CAD‡</td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia§</td>
<td>CAD,* stroke*</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td>CAD,* stroke*</td>
</tr>
<tr>
<td><strong>Inflammation, endothelial function, and other heritable factors</strong></td>
<td>CAD†, stroke‡</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>MI,* stroke†</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>MI,* stroke†</td>
</tr>
<tr>
<td>Genetic polymorphisms of PON1, eNOS, apolB, apolE, ACE, 5’ lipoxigenase, TGF-β1, and P-selectin</td>
<td>MI†, stroke†</td>
</tr>
</tbody>
</table>

---

### Table. Continued

<table>
<thead>
<tr>
<th>Inherited Hypercoagulable States</th>
<th>Association With Arterial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acquired hypercoagulable states</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>MI†, stroke,† MV†</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>MI†, stroke†</td>
</tr>
<tr>
<td>Antiphospholipid syndrome/systemic lupus erythematosus</td>
<td>CAD†, stroke†</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>CAD†, stroke†</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>MI†</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>MI†, stroke†</td>
</tr>
<tr>
<td>Myeloproliferative disorders: essential thrombocytosis, polycythemia vera, chronic myeloid leukemia and myelofibrosis</td>
<td>MI†, stroke,† MV†</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>MI,* stroke*</td>
</tr>
<tr>
<td>HRT</td>
<td>CAD†, stroke*</td>
</tr>
<tr>
<td>Pregnancy and puerperium</td>
<td>MI†</td>
</tr>
<tr>
<td>Air pollution</td>
<td>CAD†</td>
</tr>
<tr>
<td><strong>History of venous thrombosis</strong></td>
<td>CAD†, stroke†</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; PAD, peripheral arterial disease; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator; MV, microvascular disease; MTHFR, methylenetetrahydrofolate reductase; PON1, paroxysmal 1; eNOS, endothelial nitric oxide synthase; apo, apolipoprotein; and TGF, transforming growth factor.

Reported as 3 arbitrary levels of association: *probable, †possible, and‡equivocal.

§Does not denote homocysteinuria, which is an inborn error of metabolism with mental retardation and growth abnormalities.

Modified from Endler and Mannhalter,24 copyright © 2003, with permission from Elsevier.
disease, yielding a per-allele relative risk of 1.02 (confidence interval 0.97 to 1.08), 1.05 (confidence interval 0.96 to 1.13), and 1.03 (confidence interval 0.98 to 1.07), respectively. Abnormal platelet activation or aggregation has been linked to at least 3 genetic variants, including a polymorphism of the gene encoding the β-subunit of G proteins (GNB3), a dimorphism within the P2Y1 gene, and 2 haplotypes within the P2Y12 gene. In small case-control studies, genetic variation of VAMP8, which is involved in platelet degranulation, has also shown an association with early-onset MI (P=0.025), whereas the minor sequence haplotype of the GP6 gene has been associated with an increased risk of MI among elderly individuals (P=0.009).

Although not traditionally considered a hypercoagulable state, resistance to treatment with aspirin and thienopyridines represents an important potential obstacle to the management of patients with arterial thrombosis. Because pathway-specific inhibitors of platelet function are frequently used in the treatment and prophylaxis of atherothrombosis, a patient exhibiting a limited pharmacological response to these medications may be at substantial risk of recurrent atherothrombotic events. The biggest challenge to the diagnosis of antiplatelet resistance is that using different tests of platelet function, the same patient can be classified either as resistant or not resistant to antiplatelet therapy. Moreover, no randomized trials have been published that show an improvement in clinical outcomes with a strategy of modifying antiplatelet therapy according to the results of a platelet function test. Ongoing studies such as Gauging Responsiveness with a VerifyNow Assay-Impact on Thrombosis and Safety (GRAVITAS; ClinicalTrials.gov identifier NCT00645918), which has been designed to test the hypothesis that tailored antiplatelet therapy with the Accumetrics VerifyNow P2Y12 assay reduces major adverse cardiovascular events after drug-eluting stent implantation, may provide future insights into appropriate testing strategies.

Overall, these data support the existence of heritable differences in platelet biology that may increase the individual risk of atherothrombosis. Further answers may be provided by ongoing efforts of the Bloodomics consortium (www.bloodomics.org), a systems biology working group that aims to identify sequence variations in platelet genes associated with atherothrombotic risk, through the application of platelet transcriptomic and proteomic data, gleaned from functional studies in healthy volunteers, to large genotyping case-control studies of patients with the acute coronary syndrome.

The Vessel Wall

The link between atherogenic risk factors and the hemostatic system is exemplified by the biologically diverse effects of lipoprotein(a). Although proatherosclerotic effects were originally considered to account for the increased thrombotic risk in patients with elevated levels of lipoprotein(a), the discovery of its adverse effects on endothelial function, fibrinolysis, and PAI-1 levels suggests that the risk of thrombosis is mediated in part through a direct effect on the hemostatic system.

Polymorphisms of genes regulating endothelial function have been positively associated with an increased risk of atherosclerotic disease, MI, or stroke, although their specific effects on the hemostatic system remain unknown. These genetic polymorphisms include paraoxonase 1, endothelial nitric oxide synthase, apolipoprotein B, apolipoprotein E, angiotensin-converting enzyme, and 5′-lipoxygenase polymorphisms. Paraoxonase 1Q92R and endothelial nitric oxide synthase E298D polymorphisms were independently associated with onset of a first MI at age <50 years in the Thrombogenic Factors and Recurrent Coronary Events Study, which suggests a role for these genotypes in the pathogenesis of early-onset MI. More research is needed to ascertain the mechanism through which these polymorphisms influence clinical events, because it is presently unknown whether the increase in early-onset MI is caused solely by a deleterious effect on endothelial function or whether a more direct effect on hemostatic system exists.

Inflammation and Other Heritable Factors

Other risk markers for atherothrombosis not traditionally considered part of the coagulation system, including inflammatory mediators, increasingly have been shown to directly influence coagulation pathways (Table). C-reactive protein, an inflammatory marker that is increased in both asymptomatic and symptomatic arterial disease, has been found to increase macrophage tissue factor expression. The deCODE Genetics Investigators described an association between MI and a common sequence variant on chromosome 9p21 adjacent to the tumor suppressor genes CDKN2A and CDKN2B in a study of 4587 cases and 12 767 control subjects. Homozygotes for this variant had an estimated risk of MI that was 1.64 times as great as that of noncarriers, and the risk for early-onset cases was 2.02. In a study of 3657 patients with MI and 1211 control subjects, 2 specific transforming growth factor-β1 variants, the −509C/T polymorphism and −509C/868T/913G/11929C (CTGC) haplotype, were independently associated with MI in men, whereas lower risks of MI were observed among carriers of the −509CC genotype. Moreover, for MI, data exist that suggest protection for carriers of the F-selectin Pro165 allele and increased risk for specific groups carrying CD14 variants. Although preliminary and conflicting in part, the data support a possible influence of heritable nonhemostatic factors on coagulation pathways that lead to atherothrombosis.


The complexity of gene–gene and gene–environment relationships is expected to confer significant plasticity to the hypercoagulable phenotype, given that an estimated 20 000 to 25 000 coding genes exist in the human genome. The available evidence suggests strongly that coronary atherothrombosis is a complex disorder governed by multiple gene–gene and gene–environment interactions. Age contributes 1.5% to 14.5% of the observed variability in plasma hemostatic protein concentrations. The overall influence of inherited factors on arterial (and possibly venous) thrombosis is expected to decline with age, whereas acquired factors become more operational (Figure 2). However, in a study of 130 monozygotic and 155 dizygotic
same-sex twin pairs 73 to 94 years of age, genetic factors still had a major effect on variation in hemostatic protein levels, ranging from 33% for D-dimer to 71% for thrombin activatable fibrinolysis inhibitor, which suggests that heritable factors remain an important consideration in elderly individuals with suspected hypercoagulable states.

Ethnic differences in the allelic frequencies of hemostatic gene polymorphisms add another layer of complexity to deciphering the genetic basis of arterial thrombosis. The incidence of clinical thrombotic disorders varies widely between races. The Atherosclerosis Risk in Community Study reported that black individuals had a 3-fold higher multivariable-adjusted risk of lacunar stroke than white individuals. Additionally, the Multi-Ethnic Study of Atherosclerosis identified distinct profiles in hemostatic and endothelial cell markers among white, black, Hispanic, and Asian-American subjects. Black subjects had the highest levels of factor VIII, D-dimer, plasmin-antiplasmin complexes, and vWF, whereas whites and Hispanics had intermediate levels. Although Asians had the lowest levels of these markers, they also had the highest levels of PAI-1. The prevalence of several hemostatic gene polymorphisms also varies widely between ethnic groups, as noted in the Pharmacogenetic Optimization of Anticoagulation Study, which determined racial differences in prothrombotic genotype frequency among white and black patients receiving anticoagulant therapy. The factor V Leiden GA genotype was documented in 8.6% and 1.4% of white and black patients, respectively; in whites, the genotype was a significant risk factor for venous thromboembolism but not arterial thrombosis, whereas in blacks, it was an equal risk factor for both venous thromboembolism and arterial thrombosis. The implications for diagnostic testing based on race remain to be defined, and further research is needed to establish the presence of gene-ethnicity relationships.

**Acquired Hypercoagulable States**

The acquired thrombophilic disorders include uncommon but not rare conditions, such as drug-induced thrombocytopenia, autoimmune diseases, and myeloproliferative disorders (Table). In some cases, familial clustering and genetic influences are discernible (Figure 3). Pregnancy, estrogen intake, smoking, and, more recently, fine particulate air pollution can cause profound changes in coagulation. Consumption of a triglyceride-rich meal is associated with an acute elevation of factor VIIa, although it remains uncertain whether this increase depends on the actual fatty acid composition of ingested triglycerides.

**Disorders Associated With Thrombocytopenia**

Heparin-induced thrombocytopenia occurs in 1% to 3% of patients receiving unfractionated heparin for 5 or more consecutive days. Recent hospital-based registries suggest that the true incidence has been underestimated due to underrecognition in clinical practice. Although heparin-induced thrombocytopenia traditionally is associated with an increased risk of thromboembolic complications, recent data indicate that up to 6% of patients with heparin-induced thrombocytopenia may experience major bleeding. Patients developing thrombocytopenia during treatment with heparin in the Complication After Thrombocytopenia Caused by Heparin registry commonly experienced bleeding, and an increased risk of major bleeding and subsequent mortality was seen when platelet counts fell below 125 × 10^9/L.

Many patients with anti-platelet factor (PF) 4/heparin antibodies remain asymptomatic, which implies that other host-specific factors influence the development of clinical thrombosis in heparin-induced thrombocytopenia. In a mouse model transgenic for human FcγRIIa and PF4 and null for mouse PF4, mice fed a hypercholesterolemic diet and treated with an anti-PF4/heparin antibody and heparin developed more severe thrombocytopenia and more extensive thrombotic changes in platelet reactivity and endothelial activation, which suggests that diet and other host-specific factors may influence the development of thrombosis in a subset of patients who develop anti-PF4/heparin antibodies.

Thrombotic thrombocytopenic purpura (TTP) is a severe thrombotic microangiopathy characterized by profound thrombocytopenia, systemic platelet aggregation, erythrocyte fragmentation, and multiorgan ischemia. TTP must be considered in any patient receiving ticlopidine (or rarely clopidogrel) who develops a platelet count <100 × 10^9/L, and MI is an early, frequent, and severe complication of TTP. Most cases of TTP are caused by a severe functional defect of the plasma metalloprotease ADAMTS13, which fails to degrade unusually large vWF multimers. ADAMTS13 regulates platelet adhesion and aggregation through cleavage of vWF multimers. Two recent studies have demonstrated the prognostic value of inhibitory anti-ADAMTS13 antibodies in adult-acquired TTP. Patients with TTP and detectable inhibitory anti-ADAMTS13 antibodies had delayed platelet count recovery, higher plasma exchange volume requirements, and a trend toward more frequent flare-ups. High levels of inhibitory anti-ADAMTS13 IgG at presentation were associated with the persistence of an undetectable
ADAMTS13 activity in remission, the latter being predictive for relapses within an 18-month period.63

Autoimmune Disorders, Myeloproliferative Disorders, and Malignancy

The antiphospholipid syndrome is strongly associated with atherothrombosis, with several studies indicating that patients with antiphospholipid syndrome experience an increased incidence of atherosclerosis compared with the general community.64 Anti-β2-GP I antibodies bind to oxidized LDL in antiphospholipid syndrome patients and lead to enhanced uptake of oxidized LDL by macrophages in vitro.65 Anti-prothrombin antibodies have been detected in asymptomatic dyslipidemic middle-aged men and have been shown to predict MI among patients with antiphospholipid syndrome.64 Although 2 cross-sectional studies have described a 2- to 3-fold increase in the prevalence of carotid plaque or coronary artery calcification in patients with systemic lupus erythematosus,65,66 evidence supporting an increased risk of thrombosis in the absence of antiphospholipid antibodies is less strong.

The diagnostic workup for suspected antiphospholipid syndrome traditionally encompasses testing for antiphospholipid antibodies, lupus anticoagulant anticardiolipin, and anti-β2-GP I. However, in the recent Warfarin in the AntiPhospholipid Syndrome study, IgG antibodies to β2-GP I and to prothrombin were associated with anamnestic arterial and venous thrombosis, respectively, and those to annexin AV were associated with spontaneous abortions, which supports the role of anti-β2-GP I antibodies in the diagnostic workup of the syndrome and the possible role of anti-prothrombin and annexin AV antibody measurements.67

Figure 3. Pathophysiology of acquired hypercoagulable states. SNP indicates single-nucleotide polymorphism; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; anti-PF4, antiplatelet factor 4; HIT, heparin-induced thrombocytopenia; CRP, C-reactive protein; IL-6, interleukin 6; TNF, tumor necrosis factor; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; DM, diabetes mellitus; MS, metabolic syndrome; PV, polycythemia vera; ET, essential thrombocythemia; and OCP, oral contraceptive pill.
matoid vasculitis. Although MI as a direct consequence of large or medium-sized vessel vasculitis is uncommon, isolated reports of acute thrombosis within coronary artery aneurysms have been reported in patients with polyarteritis nodosa or a history of childhood Kawasaki disease, but chronic angina due to progressive arterial narrowing is by far the more common presentation of coronary or aortic arteritis.

Patients with the nephrotic syndrome, especially membranous nephropathy, have a relatively high incidence of both arterial and venous thrombosis. In an analysis of 142 patients with nephrotic syndrome and 142 matched healthy control subjects, the adjusted relative risk of MI and coronary death with nephrotic syndrome was 5.5 and 2.8, respectively. Although the actual mechanism leading to increased coronary thrombosis in nephrotic syndrome is unclear, possible pathogenic factors include hyperlipidemia, platelet hyperreactivity, endothelial dysfunction, and functional and quantitative changes in plasma coagulation proteins.

The myeloproliferative disorders often elicit unique clinical features, such as a tendency toward both hemorrhagic and thrombotic events, splenomegaly (which is occasionally massive), and clinical manifestations of microcirculatory disturbances such as ocular migraine, Raynaud phenomenon, and erythromelalgia. Thrombocytosis (>450 000 platelets/mm³) is a main feature of essential thrombocytosis and an important diagnostic feature of polycythemia vera, with concomitant increases of both erythrocyte and leukocyte cell lines in the latter disorder. The added presence of the Janus kinase-2 mutation may have important diagnostic and management implications.

Environmental Factors

Estrogen exerts numerous effects on the hemostatic system, including modulation of platelet function and endogenous levels of physiological anticoagulants. Pregnancy and oral contraceptive use are more prevalent in women with acute MI and normal coronaries than in those who have significant coronary artery disease on angiography. Acute MI occurs at a rate of 6.2 per 100 000 deliveries, which implies that in women of reproductive age, pregnancy increases the risk of MI by 3- to 4-fold. The overall contribution of plaque rupture and atherothrombosis to this rare but often catastrophic event is uncertain, and other underlying mechanisms, including vasospasm due to sympathomimetic agents and coronary dissection, have been implicated. Certain conditions, in addition to age ≥30 years, appear to be independent risk factors for MI during pregnancy and are particularly important given their modifiable nature; these include hypertension, thrombophilia, diabetes mellitus, smoking, transfusion, and postpartum infection.

The association between HRT and arterial thrombosis is particularly complex. In randomized trials including >20 000 women followed up for 4.9 years, HRT users had a significantly increased incidence of stroke and pulmonary embolism but no significant change in endometrial cancer or coronary heart disease. Psaty and colleagues suggested an interaction with other inherited hypercoagulable states and acquired risk factors, whereas Rossouw et al found that early initiation of HRT in relation to menopause might improve the risk-benefit profile. Currently, however, the weight of the evidence indicates that older women and those with subclinical or overt coronary heart disease should not take HRT.

Further data on HRT in younger women will come from the ongoing Kronos Early Estrogen Prevention Study (ClinicalTrials.gov identifier NCT00154180), which is evaluating 5 years of HRT versus placebo in 720 women 42 to 58 years of age who are within 36 months of their final menstrual period, using the prevention of progression of carotid intimal medial thickness and the accrual of coronary calcium as surrogate clinical end points.

Fine particulate air pollution has been linked to cardiovascular disease. In a study of postmenopausal women without previous cardiovascular disease who were living in cities exposed to varying levels of air pollution, each increase of 10 μg/m³ was associated with a 24% increase in the risk of cardiovascular events and a 76% increase in the risk of death due to cardiovascular disease over a 6-year period. The risk of cardiovascular disease varied with the level of exposure between and within cities. In the Intermountain Heart Collaborative Study, short-term exposure to ambient fine particulate pollution (particles with an aerodynamic diameter ≤2.5 μm) elevated by 10 μg/m³ was associated with an increased risk of acute coronary events equal to 4.5% (95% confidence interval 1.1 to 8.0), with the most pronounced effects seen in patients with angiographically demonstrated coronary artery disease. Controlled inhalation of diesel exhaust causes impairment of vascular and endothelial function in human subjects within 2 hours, and the effect persists for at least 24 hours. Although diesel exhaust exposure did not appear to affect D-dimer, platelet count, vWF, PAI-1, or C-reactive protein levels in healthy volunteers, it did suppress the acute release of endothelial tissue plasminogen activator in men with stable coronary heart disease during exercise. These studies suggest that although air pollution may potentially have a mild prothrombotic effect, its proatherogenic properties appear to have a more dominant role in mediating some of its observed adverse cardiovascular effects.

Diagnosis and Treatment of Hypercoagulable States

Diagnostic Approach to Suspected Hypercoagulable States

Patients experiencing arterial thrombotic events are more likely to have 1 or more traditional cardiovascular risk factors as a provocative stimulus rather than a rare thrombophilic disorder. This is because common atherosclerotic risk factors themselves, particularly diabetes mellitus or the metabolic syndrome, are potent mediators of thrombosis, stimulating the production of procoagulant proteins and/or impairing fibrinolysis. The presence of numerous procoagulant proteins within atheromatous plaques provides further evidence for the involvement of the hemostatic system in atherosclerosis.

Acute thrombosis can cause false-positive results when testing for hypercoagulable states that predispose to venous thrombosis: Protein C, protein S, and antithrombin activity
may be spuriously low, and factor VIII antigen or activity may be abnormally high.\textsuperscript{91} When unfractionated heparin or low-molecular-weight heparin is used, certain assays for activated protein C resistance may be unreliable, and antithrombin activity may appear abnormally low. The use of vitamin K antagonists (VKAs) may suppress protein C and S levels, as well as factor IX activity or antigen levels, although antithrombin levels may appear abnormally high. This had led to recommendations that tests for venous thrombophilia be performed a minimum of 6 weeks after the acute thrombotic event, or for subjects prescribed VKA, a minimum of 6 weeks after cessation of therapy. In contrast, tests for arterial thrombophilia are much less susceptible to the effects of acute thrombosis and can therefore be performed soon after an acute thrombotic event. Because of the highly variable effect of antiphospholipid antibodies on test reagents used to perform a test of activated partial thromboplastin time, young patients with a first arterial thrombotic event should be screened for antiphospholipid antibodies and the presence of a circulating lupus anticoagulant even in the absence of a prolonged activated partial thromboplastin time. If these antibodies are present on initial testing, tests should be repeated at a 6-week interval to ascertain persistence of elevated antibody titers.\textsuperscript{92} If patients are being treated with anticoagulants during testing for lupus anticoagulant, test kits containing neutralizers that inactivate heparin or low-molecular-weight heparin should be used.\textsuperscript{91}

A highly selected approach to genetic screening is very desirable because of the marginal effect that individual genetic polymorphisms have in determining clinical disease and a low overall detection rate. Nonetheless, the greater prevalence of several thrombophilic risk markers in selected subgroups may provide insights into disease pathophysiology and provide a personalized approach to patient care and genetic counseling.\textsuperscript{93} We recommend the algorithm modified from Andreotti and Becker, in which patients who meet any 1 of 5 criteria will undergo further testing\textsuperscript{53} (Figure 4).

DUE CONSIDERATION MUST BE GIVEN TO 2 SCENARIOS OF VENOUS THROMBOEMBOLISM THAT OCCUR WITHIN THE ARTERIAL CIRCULATION. THE FIRST IS PARADOXICAL EMBOLISM, IN WHICH THROMBOSIS OCCURS IN THE VENOUS CIRCULATORY SYSTEM HAS PROPAGATED OR MIGRATED TO THE ARTERIAL SYSTEM VIA AN INTRACARDIAC SHUNT, MOST COMMONLY A PATENT FORAMEN OVALE.\textsuperscript{94,95} PATIENTS WITH TRUE PARADOXICAL EMBOLISM REQUIRE ANTICOAGULATION WITH WARFARIN AND MAY BENEFIT FROM CLOSURE OF THE INTRACARDIAC SHUNT. THE SECOND IS SAPHENOUS VEIN GRAFT THROMBOSIS IN THE ABSENCE OF OVERT ATEROSCLEROSIS OR DEFICIENCIES OF VEIN GRAFT CONSTRUCTION.\textsuperscript{96} IT MAY BE PRUDENT TO PERFORM A COMPREHENSIVE SCREEN FOR BOTH VENOUS AND ARTERIAL THROMBOPHILIA GIVEN THE UNIQUE OPPORTUNITY FOR INTERACTION BETWEEN THE ARTERIAL AND VENOUS ENVIRONMENTS IN THESE 2 CIRCUMSTANCES.

The utility of platelet function testing remains unclear; limitations of many currently available tests include the propensity to produce in vitro artifacts and the measurement of specific markers of platelet function without providing a global estimate of platelet biology in a given subject.\textsuperscript{99} Ongoing studies of antiplatelet therapy guided by standardized point-of-care measurements may help resolve this complex issue.

**Therapeutic Perspectives**

Patients presenting with a first episode of arterial thrombosis who are subsequently found to have an inherited thrombophilic condition should receive standard treatment for the acute thrombotic episode. Family screening is recommended, and HRT should be discouraged among women found to be carriers of procoagulant gene variants.\textsuperscript{97} A treatment dilemma arises when patients with known or highly suspected arterial thrombophilia experience recurring thrombotic events. Although long-term anticoagulation with a VKA may intuitively represent an attractive treatment option, data are sparse. Most clinicians would consider long-term VKA therapy with a target international normalized ratio of 2 to 3 or aspirin-VKA combination therapy based on extrapolated data.\textsuperscript{98,99} Dual antiplatelet therapy with aspirin and a thienopyridine may be a reasonable option for events restricted to the coronary bed, although dedicated studies have not been performed in patients with arterial thrombophilia. In the future, ongoing studies to evaluate the clinical utility of assessing platelet responsiveness to antiplatelet therapy and studies examining the role of genotype-guided treatment strategies, such as the recent Randomized Trial of Genotype-Guided versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation (COUMA-GEN) study,\textsuperscript{100} may help inform selection of the appropriate antithrombotic regimen in patients with hypercoagulable states.

Despite an association between elevated serum homocysteine levels and clinical end points, no convincing evidence exists of a reduction in adverse clinical events with vitamin supplementation in patients with a modest elevation.\textsuperscript{7–10} However, it may be reasonable to implement vitamin B12, vitamin B6,
and folic acid supplementation among patients with markedly elevated homocysteine concentrations (>100 μmol/L).

The importance of recognizing acquired causes of arterial thrombophilia relates directly to the availability of beneficial treatments and management strategies for many of these conditions (Figure 5). Long-term, intermediate-intensity anticoagulation with VKA (international normalized ratio of 2.0 to 3.0) reduces the likelihood of recurrent arterial thrombosis in patients with the antiphospholipid syndrome. In essential thrombocytopenia and polycythemia vera, increased platelet biosynthesis of thromboxane A2 is suppressible by low-dose aspirin. Moreover, anagrelide or hydroxyurea added to maintenance antiplatelet therapy reduced the number of thrombotic events, compared with antiplatelet therapy without myelosuppressive therapy, in patients with essential thrombocythemia and high-risk clinical features for thrombosis.

**Future Directions**

The polygenic nature of inherited arterial thrombophilia and the complex interaction between genetic and environmental factors necessitate a paradigm shift in applied research constructs. A careful phenotypic characterization of patients is fundamental, especially when looking for new genetic risk factors. Indeed, families, which on average share a number of phenotypic traits, are the object of genetic studies par excellence. As a consequence, a distinction should be made between patients who develop an acute coronary syndrome, especially without premonitory symptoms (in which thrombosis is considered to play a pivotal role), and patients with coronary atherosclerotic disease who never develop an acute ischemic episode.

Linkage studies that use genetic markers in extended pedigrees alone may not give a complete answer because of the low penetrance of individual polymorphisms and the heterogeneity in loss-of-function mutations underlying variability within the coagulation system. Because the genetics of the coagulation system are well characterized, genome-wide association studies on large populations have emerged as an attractive platform for understanding the contribution of known single-nucleotide polymorphisms to clinical disease. The potential for deep resequencing to further fill in the gaps by identifying unknown polymorphisms may soon be realized with the availability of very-high-throughput commercial sequencing technology, such as the 454 pyrosequencing (http://www.454.com) and Solexa sequencing-by-synthesis (http://www.illumina.com) platforms. This paradigm must also be expanded to include the tremendous variability in transcription, translation, and posttranslation patterns through the use of gene expression profiling and proteomic studies. Additionally, robust analytical methods are required to reliably process large volumes of high-dimensionality data. Examples of such analytic platforms include artificial neural networks, which outperformed standard methods of regression analysis in a study testing the association between 62 single-nucleotide polymorphisms and venous thromboembolism. Investigators around the world will also be well served by the development of a strong collaborative network, such as the National Institutes of Health–sponsored Rare Thrombotic Disorders Network, to provide large data sets with sufficient imputational power.

The large sample size and systematic collection of clinical data in phase III randomized clinical trials is an attractive platform for performing parallel group mechanistic studies. The prospective acquisition of biological samples at baseline and after treatment implementation allows the use of powerful, unbiased molecular technologies, including microarray-based genome-wide genotyping and gene expression profiling, platelet proteomics, and molecular imaging, which may lead to a deeper understanding of hypercoagulable states and their appropriate treatment. Global genomic discovery efforts hold the promise of useful bench-to-bedside applications that guide patient therapy, as exemplified by the recent Food and Drug Administration approval of the Verigene F5/F2/MTHFR Nucleic Acid Test (Nanosphere Inc, Northbrook, IL) for selected patients with venous or arterial thrombosis.

**Conclusions**

The concept of arterial thrombophilia continues to evolve as the discovery of new pathways involved in human coagulation uncovers novel molecular candidates associated with a heightened risk of clinical thrombosis. Moreover, it is no longer appropriate to consider specific markers of hypercoagulability in isolation. Rather, a systems approach that accounts for the additive and possibly multiplicative effects of all potentially biologically relevant markers is preferred. In particular, better methods are needed to study the interaction
between inherited, demographic, and acquired or environmental predisposing conditions.

The vascular-bed specificity and complex genotype-phenotype relationships of hypercoagulable states mandate a selective approach to cost-effective and practical screening. An appropriate index of suspicion and carefully constructed diagnostic algorithms are essential components in the evaluation and management of patients with suspected arterial thrombophilia.

Acknowledgments

The authors thank Penny Hodgson for editorial review of the manuscript and Elizabeth Foust for her editorial assistance.

Sources of Funding

Dr Chan is supported by a medical research fellowship award from the National Medical Research Council of Singapore and by a research award from The Snyderman Foundation, Duke Clinical Research Institute.

Disclosures

Dr Chan receives research support from Regado Biosciences, Eli Lilly, and Sanofi-Aventis. Dr Becker receives research support from Regado Biosciences, The Medicines Company, Bristol-Myers Squibb, AstraZeneca, and Bayer. Dr Becker is employed by Duke University, which financed development of aptamer technology. Dr Andreotti reports no conflicts.

References


46. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, Gabriel SE. Increased unrecognized coronary heart disease...


Hypercoagulable States in Cardiovascular Disease
Mark Y. Chan, Felicita Andreotti and Richard C. Becker

Circulation. 2008;118:2286-2297
doi: 10.1161/CIRCULATIONAHA.108.778837
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/118/22/2286

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/