Special Report

Atherothrombotic Disorders
New Insights From Hematology

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How should we address the increasingly prevalent condition of arterial thrombophilia? Can arterial thromboses complicate hematological diseases or the use of antithrombotic drugs? What is POC testing? Is vascular regeneration a potential shield against atherothrombotic states? This report draws insights and perspective from the discipline of hematology to answer these and other clinically relevant questions.

Thrombophilias and Their Evaluation
The term thrombophilia can be applied to both inherited and acquired disorders that predispose to thrombosis; the 2 forms, inherited and acquired, may coexist within the same individual. Although best characterized in the context of venous thrombosis, the contribution of thrombophilias to arterial thrombosis is an area of intense investigation (Table).

Inherited Disorders of the Hemostatic System Predisposing to Arterial Thrombosis
The predisposition to venous thromboembolism among subjects with factor V Leiden (a congenital factor V resistance to cleavage by activated protein C) or with the gain-of-function G20210A variant in the prothrombin gene suggests that a fully functional system of vascular and blood-borne thromboresistance is important for venous patency. Arterial thrombosis is considered less likely to be influenced by small congenital changes in the function of hemostatic factors because it usually occurs under high shear, at sites of endothelial dysfunction/disruption or deep vessel wall injury, on a template of tissue factor–bearing cells and platelet aggregates. Notable exceptions, however, may concern individuals who develop arterial thromboses at a young age, have no obvious predisposing illnesses or cardiovascular risk factors (hypertension, diabetes, smoking, hypercholesterolemia) other than a family history of thrombosis, or have no flow-limiting artery lesions at angiography. In these groups, an increasing number of reports points to a significantly higher prevalence of thrombophilic gene polymorphisms compared with controls (Table), suggesting a biologically plausible link with arterial thrombosis. On the other hand, because the data come from highly selected groups, a survival bias cannot be excluded.

The clinical relevance of coagulation factors in arterial thrombosis is suggested by the superiority of oral anticoagulants added to aspirin (compared with aspirin alone) in the secondary prevention of acute ischemic syndromes. An additional supportive element is the finding that carriers of hemophilia A, who have mild hypocoagulability linked to reduced factor VIII levels, show a lower risk of all-cause and coronary death compared with the general female population.

In a meta-analysis of >17 000 patients with coronary, cerebrovascular, or peripheral arterial thrombotic events, the 3 most common gene polymorphisms associated with venous thromboembolism, factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T (associated with mild hyperhomocysteinemia), were identified at a slightly increased rate compared with controls. The association was stronger in patients aged <55 years and in women.

For individuals with venous thromboembolism, presentation at a young age or with no apparent cause has long prompted the search for (and discovery of) a number of congenital thrombophilias (Table). By the same token, it seems reasonable to look for inherited thrombophilias in subjects with arterial thrombosis who are young or have no apparent reason for their vascular event.

It is important to realize, however, that among unselected patients, the frequency of the polymorphisms listed in the Table is usually not significantly different from that in controls. In unselected cases, the frequency of these polymorphisms becomes diluted by the presence of other prothrombotic conditions, which are more prevalent and probably stronger (such as advancing age, traditional cardiovascular risk factors, underlying atherosclerosis, other comorbidities), and by genetic heterogeneity (ie, different genetic backgrounds producing apparently similar phenotypes). Thus, the number of patients in whom some of the currently known hemostatic gene polymorphisms may play a predisposing role represents only a minority of the entire population with acute ischemic syndromes. For this reason, screening for thrombophilic gene variants is not warranted in all patients but may be considered for those in whom the likelihood of a detectable genetic predisposition is increased (Figure 1). In the clinical relevance of coagulation factors in arterial thrombosis is suggested by the superiority of oral anticoagulants added to aspirin (compared with aspirin alone) in the secondary prevention of acute ischemic syndromes. An additional supportive element is the finding that carriers of hemophilia A, who have mild hypocoagulability linked to reduced factor VIII levels, show a lower risk of all-cause and coronary death compared with the general female population.

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phisms may increase as much as 5-fold compared with controls, reaching 12-fold increases in the case of combined carriership. On the other hand, there is also evidence that inherited thrombophilic states play a significant role precisely among patients with a low a priori cardiovascular risk profile (eg, young, female, without traditional cardiovascular risk factors). In these cases, it is conceivable that as yet unrecognized or poorly appreciated genetic and/or acquired/environmental conditions interact with the known inherited variants to promote arterial thrombosis. In accordance with this view, severe thrombophilia on the venous side is increasingly regarded as a model of multigenic disease.

### Acquired Disorders Predisposing to Arterial Thrombosis

Cardiologists, whether in an ambulatory setting or in the hospital, should keep in mind a number of acquired conditions—attributable to systemic illnesses, malignancies, and/or offending drugs and environments—that predispose to thrombotic events (Table). What follows is a selection of conditions, specifically drawn from hematology, that are often poorly addressed by cardiologists.

Thromboses associated with acquired thrombophilias may occur in the venous, arterial, and/or microcirculatory systems and may cause a “burst,” “storm,” or “crisis” of thrombotic events at multiple sites, concomitantly or in rapid succession. This devastating presentation is most common with heparin-induced thrombocytopenia and with the “catastrophic” manifestation of the antiphospholipid syndrome (an acute, multiorgan, thrombotic microangiopathy carrying a 50% mortality rate).
rate). Accordingly, rapid evaluation and intervention are critical for achieving optimal patient outcomes.

### Antiphospholipid Syndrome and Systemic Lupus Erythematosus

The antiphospholipid syndrome and systemic lupus erythematosus (SLE) are autoimmune disorders strongly associated with atherosclerotic vascular disease and arterial thrombosis. The antiphospholipid syndrome is defined by the presence of at least 1 of 2 clinical criteria (vascular thrombosis or specific complications of pregnancy) combined with at least 1 of 2 laboratory criteria (related to IgG/IgM anticardiolipin antibodies or to lupus anticoagulant antibodies, globally called antiphospholipid antibodies). In SLE, damage to single organs or multiple systems is caused by the deposition of immune complexes and pathogenetic autoantibodies (which may include antiphospholipid antibodies). The prevalence of antiphospholipid antibodies is estimated to be 1% to 5% in young, apparently healthy subjects. The rate increases with age and coexistent chronic illnesses, reaching 15% to 30% among patients with SLE. SLE shows a strong predilection for women.

A number of prospective studies have related the presence of antiphospholipid antibodies to subsequent myocardial infarction (MI) and stroke. Two recent cross-sectional investigations described a 2- to 3-fold increase in the prevalence of carotid plaque or coronary artery calcification in patients with SLE compared with matched controls, independent of the traditional cardiovascular risk factors. The thrombotic manifestations of SLE and the clinical features of the antiphospholipid syndrome are related to thromboembolic events most commonly involving the venous system but also the microcirculation or arteries of the brain, heart, and gastrointestinal tract. Virtually any organ may be affected.

Antiphospholipid antibodies are directed toward phospholipid-binding proteins and, in particular, the plasma protein β2-glycoprotein I. Their prothrombotic properties are impressively diverse and include attenuation of activated protein C, downregulation of antithrombin III, inhibition of the anticoagulant activity of β2-glycoprotein I, endothelial cell activation, enhanced binding of prothrombin to biological surfaces, enhanced adhesion molecule expression, platelet activation and aggregation, and impaired fibrinolysis.

Young women with SLE additionally show elevated levels of circulating apoptotic endothelial cells, correlated with abnormal endothelial function and with raised plasma levels of tissue factor. Young patients with a first thrombotic event should be screened for antiphospholipid antibodies even in the absence of the typically prolonged activated partial thromboplastin time (Figure 1). Long-term, intermediate-intensity anticoagulation with warfarin (international normalized ratio [INR] of 2.0 to 3.0) is appropriate to prevent recurrent thrombosis.

### Myeloproliferative Disorders

Polycythemia vera (characterized by splenomegaly and increased production of all myeloid elements), essential thrombocythemia (characterized by thrombocytosis, splenomegaly, and giant platelets), chronic myeloid leukemia, and myeloid metaplasia/myelofibrosis constitute the group of myeloproliferative disorders. These conditions have in common a hemostatic imbalance that predisposes patients (particularly those with polycythemia vera or essential thrombocythemia) to both hemorrhagic and thrombotic events. Bleeds typically involve mucocutaneous sites (bruising, epistaxis, gingival bleeds), suggesting abnormal platelet plug formation. When treated with antiplatelet agents, these patients are at increased risk of bleeding. Thrombosis may involve virtually any site of the venous, arterial, and/or microcirculatory districts.
normal arteriograms and in the absence of traditional cardiovascular risk factors, whereas microvascular disturbances may lead to ocular migraine. Raynaud’s phenomenon, or erythromelalgia. Compared with secondary (reactive) forms, the primary forms of both polycythemia and thrombocytosis are associated with a far greater thrombotic risk.

In patients with polycythemia vera, the risk of thrombosis has been attributed, at least in part, to the increased blood viscosity caused by raised hematocrit values. Patients with essential thrombocythemia, on the other hand, have a normal hematocrit. Thrombocytosis (>450,000 platelets/mm$^3$) is a main feature of these 2 disorders and may contribute to the microcirculatory disturbances; otherwise, the correlation between total platelet count and thrombosis is poor.

Causes of secondary (reactive) thrombocytosis should be sought and excluded, the most common being tissue damage from major surgery, infection, cancer, and chronic inflammation. In polycythemia vera, the serum levels of erythropoietin are low. In both diseases, platelet abnormalities have been identified that cause reduced hemostatic effectiveness, on the one hand, and increased platelet activation in vivo, on the other. An increased biosynthesis of thromboxane A$_2$ has been reported, suppressible by low-dose aspirin and thus suggestive of a platelet origin. A recent randomized trial in patients with polycythemia vera demonstrated the safety and efficacy of low-dose aspirin in preventing both venous and arterial thromboses over a period of 3 years.

**Thrombophilias Induced by Antithrombotic Drugs**

**Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated disorder that should be suspected when the platelet count falls to <150,000/mm$^3$ or <50% of baseline values during or up to 3 weeks after treatment with heparin. Its incidence is calculated at ≈3%, but this may be an underestimation. Whenever possible, the suspicion should be confirmed by laboratory testing (ie, positivity for the presence of heparin-related antibodies by antigen assay or by a functional platelet-based assay) because nonimmune HIT is not uncommon. The latter is associated with a more modest decrease in the platelet count and a lack of thrombotic manifestations.

In selected groups, heparin-related antibodies can develop in up to 50% of treated patients in the absence of thrombocytopenia or thrombosis. HIT may develop with any dose or form of heparin (including heparin-coated indwelling vascular catheters), although it is more common with unfractionated heparin compared with low-molecular-weight forms. The onset typically occurs ≈4 days after the start of therapy, but, in patients who have received heparin within the previous 3 months, it may arise within the first hours. The development of antibodies (usually IgG) against circulating heparin–platelet factor 4 complexes leads to platelet activation, procoagulant activity, and endothelial damage. These antibodies are transient and tend to disappear over a period of 3 months. The platelet count recovers into the normal range within several days of heparin cessation.

Thrombosis, which occurs in ≈25% of patients with HIT, may involve the venous, arterial, and microvascular circulation. Venous thromboembolism is more common than arterial thrombosis; however, the latter may have devastating, life-and limb-threatening clinical consequences. Mortality, once thrombosis develops, may be as high as 50%. Careful monitoring, prompt recognition, immediate heparin withdrawal, and correct use of danaparoid (a factor Xa inhibitor) or of direct thrombin inhibitors are crucial for proper management. Warfarin should be avoided because of its early prothrombotic potential caused by the rapidly induced decrease of anticoagulant protein C activity.

**Thienopyridines and Thrombotic Thrombocytopenic Purpura**

Thrombotic thrombocytopenic purpura (TTP) is a severe thrombotic microangiopathy characterized by profound thrombocytopenia, systemic platelet aggregation, erythrocyte fragmentation, and organ ischemia. Most cases of TTP are probably caused by failure to degrade unusually large von Willebrand factor multimers as a result of a severe defect in the function of a plasma metalloprotease (ADAMTS-13) that normally cleaves the hyperreactive, ultralarge von Willebrand factor multimers into smaller, less adhesive forms. Clopidogrel, a widely used platelet ADP receptor antagonist, has a favorable safety profile. Although clopidogrel-related TTP has been reported, its occurrence (11 cases per 3 million patients treated) is rare. Nevertheless, TTP is a potentially life-threatening disorder and must be considered in any patient receiving clopidogrel (or ticlopidine) who develops a platelet count <100,000/mm$^3$.

**The Basis for Further Investigation**

**Whom to Investigate**

In patients with arterial thrombosis, the search for an underlying thrombophilic condition is justified in the presence of at least 1 of the following: (1) recurrent thromboembolic event; (2) young age (≤50 years if male, ≤55 years if female); (3) lack of significant artery stenoses at angiography; (4) age ≤55 years if male or ≤60 years if female and no apparent cause (ie, lack of traditional cardiovascular risk factors, systemic illnesses, malignancies, offending drugs); or (5) age ≤55 years if male or ≤60 years if female and strong family history of thrombosis (Figure 1). The importance of gathering a family history, a simple and frequently underutilized tool available to all and useful in assessing the risk for common complex diseases, has been stressed by the Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention.

**What and When to Investigate**

The tests shown in Figure 1 may be performed during hospitalization, even during the initial stages of a thrombotic episode. Evaluations for an acquired thrombophilia, including those associated with underlying malignancy, systemic disorders, and drug-induced prothrombotic states, should also begin without delay. A definitive diagnosis of myeloproliferative disorder or the search for occult malignancy may require serial office visits and investigations.
Implications for Treatment
The approaches to inherited and acquired thrombophilias differ at several levels. The former raises questions of susceptibility to recurrent events, treatment duration, and whether to perform testing among related family members (who may themselves carry the trait).36 The latter is based on concomitant illnesses and identification of offending drugs or conditions in which diagnosis and treatment of the predisposing disorder have a major impact on the overall thrombotic risk.

New Point-of-Care Testing
The ability to make rapid decisions based on readily available and accurate information is a cornerstone of optimal patient care. The development of bedside assays and alternate testing sites, referred to as point-of-care (POC) tests, has provided a means for clinicians in emergency or other cardiovascular arenas to manage a variety of thrombotic disorders. The general goal of POC tests is to titrate the dosing of antithrombotic drugs to the patient’s individual response to achieve a range that consistently surpasses a lower threshold of efficacy but does not exceed an upper boundary of safety. Certain subgroups, including the elderly, women, and those with impaired renal or liver function, should derive special benefit.

Monitoring Global Coagulation
POC-coagulation monitors that measure whole blood prothrombin times (PT), activated partial thromboplastin times (aPTT), and activated clotting times (ACT) are widely used in anticoagulation clinics, coronary care units, catheterization laboratories, operating rooms, and, more recently, the home setting.37-39 These methods are considered the standard of care during cardiopulmonary bypass and percutaneous coronary interventions, and they are rapidly gaining acceptance in ambulatory practices to expedite decision making and to avoid prolonged delays (and patient dissatisfaction) awaiting the results from central laboratories.

Prothrombin Time and International Normalized Ratio
For patients receiving warfarin, the PT is best expressed as the INR.40 The INR is calculated automatically through an index that equilibrates the thromboplastin used in the patient’s assay against an international reference thromboplastin. The INR is essentially the PT ratio (the patient’s PT divided by the mean of the normal range) obtained if the international reference thromboplastin had been used. Most cardiac conditions requiring warfarin therapy are adequately treated at INR values between 2.0 and 3.0; patients with mechanical heart valves, especially in the mitral position, may benefit from higher values (up to 3.5).

Activated Partial Thromboplastin Time
For patients with acute MI receiving intravenous unfractionated heparin, an aPTT range of 50 to 70 seconds is recommended because this range is associated with the lowest probability of adverse events compared with shorter or longer times.41

Activated Clotting Time
ACT measurements are performed to monitor unfractionated heparin therapy during coronary angioplasty and bypass surgery. During angioplasty, values <250 seconds are associated with an increased incidence of major complications.37 Administration of the platelet glycoprotein IIb/IIIa inhibitor abciximab prolongs the ACT by ~35 seconds.38

Monitoring Anti-Xa Agents
The widespread use of low-molecular-weight heparins in the management of patients with venous and arterial thrombotic disorders has stimulated interest in bedside monitoring of anti-Xa agents to assist with dose titration and to define a “therapeutic” level of anticoagulation. A rapid POC assay for enoxaparin using citrated whole blood (Enox time) has been approved by the Food and Drug Administration. In a study of 445 patients who received either subcutaneous or intravenous enoxaparin before percutaneous coronary intervention, a range of Enox times between 250 and 450 seconds (which correlated with anti-Xa levels between 0.8 and 1.8 IU/mL) was associated with a trend toward a reduced composite occurrence of death, MI, and target vessel revascularization.42 Elevated Enox times were associated with an increased risk of bleeding at the time of sheath removal.42 The role of anti-Xa monitoring in routine patient care remains to be determined, however.

Monitoring Platelet Function
Assessing platelet performance has traditionally been undertaken with turbidimetric or, less commonly, impedance platelet aggregometry, a lengthy and complex laboratory test performed by specially trained technicians. Several whole blood POC instruments, including the platelet function analyzer (PFA-100), simulate primary hemostasis under high-shear-stress conditions and have been used in different clinical settings.43 The rapid platelet function assay44 is a semiautomatic turbidimetric system based on the ability of activated platelets to interact with fibrinogen, yielding macroscopically visible agglutination. Although the device was originally developed to gauge platelet inhibition by glycoprotein IIb/IIIa receptor antagonists,44 variations in this method may prove to be useful in determining resistance to aspirin and clopidogrel. As with anti-Xa monitoring, further clinical investigation will be required to more clearly define the role of these emerging instruments in routine patient care.

Therapeutic Advances
Atherothrombosis and Progenitor Cells
Vascular cell apoptosis is considered a crucial step in the development of atherosclerosis and thrombosis.45-47 Conversely, the resilience of the vessel wall, ie, its “youthful” capacity to achieve rapid and complete self-repair, may be fundamental to prevent atherothrombotic disorders. The resilience of injured endothelium has been related to the availability of endothelial progenitor cells (EPCs) because these cells can re-endothelialize sites of vascular injury.48 The number of circulating EPCs, in turn, depends on the capacity of the bone marrow to produce precursor cells—in response to factors such as vascular endothelial growth factor.
erythropoietin, and insulin-like growth factor 1 (IGF-1)—and to release them into the bloodstream. EPC mobilization from the bone marrow requires endothelial nitric oxide (NO) synthase. Thus, NO (which is typically reduced in atherothrombotic states or in the presence of cardiovascular risk factors) and progenitor cell–stimulating factors may conceivably help to halt atherothrombosis by promoting vascular resilience (Figure 2).

Elements supporting a role for healthy vascular regeneration in the prevention of atherothrombosis include the direct relation between preserved endothelial function and circulating EPCs, the beneficial effects of vascular endothelial growth factor against arterial restenosis, the prediction of ischemic events by reduced circulating levels of IGF-1 and by renal impairment (a state of low IGF-1 and erythropoietin production), and the lack of clinical benefit of somatostatin analogues (growth factor inhibitors) in patients with ischemic heart disease. Tissue injury and ischemia can cause increased plasma concentrations of these growth factors. Thus, raised levels may represent a secondary reaction to tissue damage rather than active players in the onset of disease. Whether strategies aimed at enhancing an individual’s regenerative potential will reduce the burden of atherothrombotic disorders remains to be seen.

Aptamers or Protein-Binding Oligonucleotides

Aptamers are single-stranded nucleic acids that inhibit the function of a protein by folding into a specific 3-dimensional structure that dictates high-affinity binding to the target protein. The term aptamer (from the Latin aptus [bound]) was coined by Ellington and Szostak after their pioneering work originally published in Nature. On the basis of iterative selection techniques, aptamers that bind to essentially any protein or small molecule can be generated. Moreover, high-affinity, specific inhibitors that interact with functional groups on both the nucleic acid and the protein can be constructed if a small amount of pure target is available.

The starting point for aptamer development is a combinatorial library composed of single-stranded nucleic acids...
(RNA, DNA, or modified RNA), typically containing 20 to 40 randomized positions ($10^2$ to $10^4$ different sequences). The isolation of high-affinity nucleic acid ligands requires purification by a process known as SELEX (Systematic Evolution of Ligands by EXponential enrichment). The starting library is incubated with the protein of interest. Nucleic acid molecules that adopt conformations that allow target protein binding are subsequently identified and separated from other sequences that do not bind the protein. The bound sequences are removed and amplified by reverse transcription and polymerase chain reaction for RNA-based libraries or by polymerase chain reaction alone for DNA-based libraries. After the process has been repeated several times, the selected ligands are sequenced and evaluated for binding affinity and ability to inhibit the activity of the target protein (Figure 3).

Postselection optimization steps include reduction of aptamer length, from a starting molecule of 80 to 100 nucleotides to 40 nucleotides; enhancement of stability in biological systems and protection from exonuclease digestion; and reduced renal clearance, achieved by increasing the molecule’s molecular weight through site-specific addition of polyethylene glycol moieties or other hydrophobic groups.

A 15-nucleotide DNA aptamer directed toward thrombin inhibited fibrin clot formation in vitro with the use of purified fibrinogen or human plasma. Subsequent studies employing a constant infusion (because of a 1- to 2-minute plasma half-life) identified the ability of the aptamer to maintain patency of an extracorporeal circulation model in sheep and dogs.

A combinatorial library was used to isolate a high-affinity, nuclease-resistant, RNA ligand that bound specifically to factor VIIa, preventing its complexing with tissue factor. The factor VIIa aptamer prolonged tissue factor–induced clotting times of human plasma in a concentration-dependent manner and was stable, with a circulating plasma half-life $>15$ hours. An aptamer against factor IXa, exhibiting a specificity to this protein more than 5000 times greater than its specificity to structurally similar coagulation proteases (factor VIIa, factor Xa, factor XIa, and activated protein C), inhibited the activation of factor IXa on a liposome surface and prolonged the aPTT in human plasma. An oligonucleotide complementary to the aptamer, altering its shape from an active to an inactive conformation, completely attenuated the anticoagulant effect (drug-antidote pair construct) in vitro and in plasma derived from patients with HIT (Figure 4).

Clearly, the ability to design inhibitors against specific coagulation proteases, as well as their direct antidotes, provides an opportunity to pursue patient-specific therapeutics that can be regulated. Phase II trials have been planned.

**Conclusion**

As knowledge of atherothrombotic states progresses, it is likely that the largely unpredictable, often elusive, heterogeneous, and multifactorial nature of these disorders will begin to unravel in parallel with the solidity of our working hypotheses, the availability of improved investigational tools, and the refinement in the definitions of clinical phenotypes. This should lead to a more accurate recognition of individual disease expressions and treatments. Hematology has contributed—and will undoubtedly continue to contribute—greatly to the understanding of both atherosclerosis and thrombosis.
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References


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