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Venous Thromboembolism Risk Factors, Biomarkers, and Treatment

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In 2005, the U.S. Senate declared March as deep vein thrombosis (DVT) awareness month. This is the second year in which we have highlighted this event with a collection of 6 articles in *Arteriosclerosis, Thrombosis, and Vascular Biology* focused on DVT. It is estimated that 2 million Americans per year develop DVT, which is associated with life-threatening pulmonary embolism (PE). DVT and PE are collectively termed venous thromboembolism (VTE). Despite the large number of cases, a survey conducted by the American Public Health Association in 2002 found that 74% of Americans were unaware of venous thrombosis.¹

The risk of VTE increases with thrombophilias, age, pregnancy, and comorbidities, including cancer and antiphospholipid syndrome (APS). It has not yet been determined whether similar mechanisms lead to VTE in each of these disorders. The articles in this issue describe current research into disorders associated with increased VTE risk, including potential pathophysiologic mechanisms, treatment of these clinical situations, and a review on biomarkers for the detection and prevention of VTE.

The first article by Zhu et al,² entitled “Venous Thromboembolism: Risk Factors for Recurrence,” summarizes our current knowledge of the risk factors for recurrent VTE. This is an important issue because they influence the intensity and duration of anticoagulation therapy in different patients. The authors point out that VTE should be considered a chronic rather than acute illness because resolution of venous clots may take several weeks to months. These patients may also develop postthrombotic syndrome. They conclude that more studies are required to establish good biomarkers that predict VTE in the different patient populations.

An original article in this series by Jang and colleagues,³ entitled “Metabolic Syndrome Is Associated With Venous Thromboembolism in the Korean Population,” reports findings on a case-controlled study. Metabolic syndrome (MS) is a cluster of pathologies (abdominal obesity, hypertension, insulin resistance, dyslipidemia, and low HDL) that has previously been linked to atherosclerotic risk in several groups. However, the association between MS and VTE has only previously been reported in whites. The prevalence of MS in VTE patients in the Korean population compared to healthy controls strongly implicates this disorder in the etiology of idiopathic VTE in this population. However, the broader implications of this work stem from observations of the increase in incidences of both MS and VTE in the general population. MS may be a common pathogenic mechanism for the development of VTE, representing an

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important facet in the identification of patients at risk for VTE, as well as in studies into the causes and prevention of VTE.

Cancer patients account for as many as 20% of the total burden of VTE in the general population. The article by Sousou and Khorana,⁴ entitled “New Insights Into Cancer-Associated Thrombosis,” summarizes current thinking about risk factors and pathological mechanisms contributing to VTE in cancer patients. Considerable effort has focused on the role of tissue factor (TF) in cancer and VTE development, although studies suggest that other molecules, such as plasminogen activator inhibitor type 1, mucins, and proinflammatory cytokines, may have a causative role in cancer-related VTE. Some risk factors and comorbid conditions associated with cancer-related VTE are similar to those reported for other conditions, for example, obesity, hospitalization, and major surgery. However, other risk factors are unique to cancer, including the primary site of the cancer and the nature of the chemotherapy used during treatment. Treatment and prevention of VTE in cancer patients is similar to that in noncancer patients, although bleeding risks may be somewhat higher. Moreover, the authors note that low-molecular-weight heparins may also reduce tumor growth and metastasis, suggesting a unique effect of VTE management in this population. One of the authors has recently published a risk model for chemotherapy-associated VTE. This model forms the basis of a new study of the effect of thromboprophylaxis on the rate of VTE in high-risk cancer patients.

APS is one of the most common and yet poorly understood causes of thrombosis. It is associated with both arterial and venous thromboembolism, as well as recurring pregnancy loss. The list of pathological mechanisms proposed for APS is long and invokes both soluble and cellular pathways. The article in by Farmer-Boatwright and Roubey,⁵ entitled “Venous Thrombosis in the Antiphospholipid Syndrome,” discusses basic pathophysiology associated with the development of APS, including caveats associated with the diagnosis, nomenclature, and classification of APS. Strong correlative epidemiological data suggest that antiphospholipid antibodies are a causative agent in the development of VTE, and animal studies of antiphospholipid antibody-mediated VTE strongly support this premise. As in other VTE-associated disorders, a spectrum of factors including hormone therapy, smoking, and inherited thrombophilia appear to further increase thrombosis risk for APS patients. Long-term moderate-intensity anticoagulation with warfarin is the current standard of care for treating and preventing of VTE in APS; however, monitoring the international normalized ratio in APS patients is associated with additional caveats because of the anticoagulant nature of APS-associated antibodies in laboratory tests.

The fascinating irony of pregnancy-related hypercoagulability and VTE is that genetic and acquired hypercoagulability in pregnancy likely evolved as a beneficial mechanism to prevent hemorrhage during miscarriage and delivery. Yet in Westernized countries with capable management and prevention of hemorrhage, VTE has become the leading cause of maternal death. The article by James,⁶ entitled “Venous Thromboembolism in Pregnancy,” summarizes aspects of VTE in pregnancy, including genetic and acquired risk factors for VTE in pregnancy. It describes strategies used to prevent VTE during pregnancy and after delivery, and makes treatment recommendations for managing maternal DVT and PE, while protecting the health of the developing fetus. Because there have been no large trials of anticoagulants in pregnancy, this article notes that recommendations are based on case series and opinion, perhaps issuing a call to action for clinical trials and the identification of evidence-based recommendations for VTE in pregnancy.

In all of the cases above, a primary goal of current efforts in VTE research is to identify specific biomarkers for the identification of patients at risk of primary and recurrent VTE. In the article by Pabinger and Ay,⁷ entitled “Biomarkers and Venous Thromboembolism,” data are

presented on a subset of proteins that have been evaluated as potential biomarkers of VTE. The list includes established biomarkers currently used in the diagnosis of VTE (D-dimer and factor VIII levels), as well as novel markers that have not yet been established as clinically meaningful, including P-selectin levels and thrombin generation. The authors note that the positive and negative predictive value of each of these measures is currently limited. For example, although the most widely-used of these markers, D-dimer, has a strong negative predictive value (nearly 100%) for both DVT and PE, its limited specificity reduces its value as a reliable predictor of recurrent events, especially in the elderly. Thus, the utility of each of these proteins as predictive biomarkers may be most effective when used as one element of a “comprehensive, sequential, diagnostic strategy” that incorporates multiple techniques.

In spite of these advances in the identification of VTE risk factors and biomarkers and development of novel anticoagulants, the high morbidity and mortality associated with VTE speak to how much progress is still needed to understand the mechanisms contributing to VTE in different clinical scenarios. Certain common molecular and pathological mechanisms have been implicated in VTE in several comorbid disorders. However, unique treatment considerations in each case make it unlikely there will be a single “magic pill” that can treat or prevent VTE in all cases. Clearly, much work is needed.

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