Article in this series


**Update on Venous Thromboembolism**

**Risk Factors, Mechanisms, and Treatments**

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Deep vein thrombosis (DVT) and pulmonary embolism, collectively called venous thromboembolism (VTE), are a public health crisis. The number of incident and recurrent VTE events is estimated at more than 1 million per year.1 Beyond the initial risk of death, estimated at greater than 30% within 30 days of the event, one third to one half of surviving patients develop recurrent thrombosis or long-term morbidity associated with post-thrombotic syndrome.2,3 The economic burden of VTE is substantial; treatment of a single VTE event costs from $10 000 to more than $16 000 per person.4 Consequently, each year more than $2 billion dollars is spent on VTE treatment, attributable to costs associated with both new and recurrent events.4 Moreover, the impact of VTE is increasing with the growing aging population; risk rises from 1/10 000 at birth to 1/100 in individuals older than 80 years.1 Because pulmonary embolism risk rises faster than DVT, the relative incidence of pulmonary embolism, and therefore the fatal impact of VTE, also increases with age.1,2 Clearly, the health and economic burden of VTE is profound, and the need for improved understanding and treatment is essential.

In 2005, the United States Senate designated March “Deep Vein Thrombosis Awareness Month.” A PubMed search for “deep vein thrombosis” or ‘pulmonary embolism’” in the 5 years before (2000 to 2004) versus the 5 years after (2005 to 2009) this designation reveals that publications increased ≈17% following the Senate’s call. Of particular note are the more than 900 publications from clinical trials of VTE prevention and treatment between 2005 and 2009, underscoring the impact of VTE in the translational arena. Unfortunately, however, clinical progress is still limited by a deficit in understanding of the etiology and pathogenesis of this disease.

To support the continued focus on basic, clinical and translational investigation in VTE, *Arteriosclerosis, Thrombosis, and Vascular Biology* is again publishing its annual issue focused on VTE. In this special issue, we have assembled a collection of articles summarizing the state of the field of VTE research, including risk factors for common and rare forms of VTE, molecular mechanisms of fibrin formation, computational approaches to understanding thrombus development, the immunologic response to thrombosis, and thrombus treatment and resolution. Each of these articles reviews current knowledge and identifies areas in need of further investigation.

Epidemiological studies have provided substantial information correlating common and rare risk factors with VTE. In their article “Hypercoagulation and hypofibrinolysis in the etiology of common and rare venous thrombosis: deep vein thrombosis versus splanchnic vein thrombosis,” Smalberg et al review these risk factors in both common and rare presentations of venous thrombosis, with a particular focus on Budd-Chiari syndrome and portal vein thrombosis. The unique and differently weighted risk factors for these tissue and vessel-specific forms of venous thromboses simultaneously underscore the complexity of the VTE etiology and provide clues to the underlying pathophysiologic mechanisms. As-yet-identified local factors affecting vascular bed function are likely important.
variables in these processes; elucidating these factors will require novel approaches that enable simultaneous evaluation of vascular function with plasma abnormalities. Although it has been notoriously difficult to study native vascular (endothelial) function ex vivo, emerging technologies enabling studies of cellular function under blood flow will certainly shed light on the role of the vascular bed and stasis in VTE.

Venous thrombi are fibrin rich, indicating that fibrin formation lies at the heart of VTE development. Numerous studies have demonstrated abnormal fibrin formation, structure, and stability in plasma clots from thrombosis patients. Importantly, fibrin remains the only therapeutic target for dissolving both arterial and venous thrombi in the acute setting. The review “Molecular mechanisms affecting fibrin structure and stability” by Dr Susan Lord provides a detailed description of fibrinogen conversion to fibrin and subsequent fibrinolysis, with a particular focus on fibrinogen variants and their effect of fibrin formation, strength and structure. Dr Lord also discusses recent studies that demonstrate the remarkable mechanical properties of fibrin fibers; fibrinogen’s unique physical structure affords fibrin extraordinary elasticity and extensibility. Importantly, this article highlights the etiologic role of the fibrin network structure in VTE. There remain, however, important unanswered questions, including uncertainty regarding the mechanisms that mediate lateral aggregation, factor XIII activation, and the nature of plasminogen’s interaction with the fibrin network. Improved understanding of these mechanisms will further define the link between fibrin structure and thrombotic disease and may be useful in assessing VTE risk from plasma clot samples.

Understanding the mechanistic role of these plasma and cellular risk factors on thrombus development will ultimately require quantitative appreciation of the effects of these abnormalities on platelet function, thrombin generation, and fibrin formation. Although biological and biochemical experiments have provided most of the information currently known about clot formation, in silico modeling holds promise for understanding quantitative aspects of coagulation with higher spatial and temporal resolution than currently measurable in vitro or in vivo. In their article “Computational approaches to studying thrombus development,” Xu et al review the current status of these in silico approaches and their potential to enhance understanding of thrombotic mechanisms. Validated by agreement with aspects of the biological findings, computational approaches focused on individual facets of coagulation (enzyme pathways, fibrin polymerization, platelet activation) are maturing to integrated, multiscale models of thrombogenesis. Recent computational studies have generated biologically testable hypotheses regarding effects of coagulation factor levels on thrombus formation, shear stress–mediated embolization, and effects of platelet number and distribution on a growing thrombus. Ideally, integration of in silico, in vitro, and in vivo methods will permit nano- to macroscale understanding of mechanisms operant in coagulation pathologies.

Increased information on mechanisms promoting thrombosis has given rise to a new appreciation for the role of inflammation in venous thrombus resolution. The article by Saha et al titled “Leukocytes and the natural history of deep vein thrombosis: current concepts and future directions” discusses the role of inflammation in both thrombus formation and thrombus resolution. In particular, the complex roles of polymorphonuclear neutrophils and monocytes/macrophages are described with an emphasis on temporal recruitment and regulation of these cells. Although these 2 cell types have some overlapping putative functions, including fibrinolysis, chemokine and cytokine production, and phagocytosis, the authors note unique functions for each. Polymorphonuclear neutrophils facilitate vein wall remodeling, whereas monocytes and macrophages are involved in wound healing and clearance of red blood cells. Interestingly, the induction of inflammation caused by red blood cells within a growing thrombus is also described. Saha et al highlight areas in need of further study, including leukocyte signaling and approaches to therapeutically target polymorphonuclear neutrophils and monocytes/macrophages during thrombus formation and resolution.

Beyond the initial risk of embolization from DVT, morbidity from postthrombotic syndrome develops in 25% to 50% of DVT patients and results in chronic pain and swelling in the affected limb, greatly reducing quality of life. In their article “The role of thrombolysis in the clinical management of deep vein thrombosis,” Popuri and Vedantham provide a comprehensive overview of the etiology of postthrombotic syndrome. Highlighting the “open vein hypothesis” which correlates improved clinical outcome with rapid thrombus removal, Popuri and Vedantham review current approaches to thrombolytic therapy. Of particular interest are recent developments in endovascular thrombolytic techniques, which use a catheter or thrombectomy device to deliver thrombolytic drugs directly to the thrombus. Although several small studies suggest that these new approaches increase specificity and safety (reduced risk of bleeding) over traditional intravenous thrombolysis, the authors note the lack of prospective randomized clinical trials evaluating endovascular DVT thrombolytic techniques. Popuri and Vedanthan highlight 2 ongoing trials—CaVenT and ATTRACT—that are expected to provide efficacy and safety data on these new approaches within the next 2 to 5 years. Pending completion of these trials, the most important issue facing clinical management of VTE patients is determining whom to treat with thrombolytic therapy; Popuri and Vedantham present a series of considerations balancing the risk of bleeding, benefit of treatment, and patient preferences.

Although this collection of articles spans epidemiological, basic, and clinical aspects of VTE, common themes emerge. As expected, the articles acknowledge the established triad of risk factors implicating plasma hypercoagulability, vascular wall dysfunction, and stasis in the etiology of VTE. Perhaps more importantly, however, these articles also highlight newer data on the contributions of inflammatory cells, cell-derived procoagulant microparticles, and fibrin biochemical and biophysical properties to VTE, suggesting additional interplay of plasma, cellular function, and stasis in the pathophysiology of thrombosis. Each of these represents a new avenue of investigation for novel, targeted therapeutic options. Fundamentally, the goals to accelerate resolution of existing VTE and, ultimately, to prevent primary and recurrent VTE depend on choreographed efforts from basic researchers and clinicians. Progress since the 2005 Senate resolution looks promising.
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References

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