Hemostasis, the arrest of bleeding, requires a finely tuned balance between clot formation and clot degradation. Platelets provide the first line of defense when vascular integrity is compromised. They home to the site of injury where they adhere to the damaged vessel wall, become activated and aggregate to form a platelet plug.

The second line of defense involves the strengthening and stabilization of the platelet plug by fibrin strands, which tie the platelet aggregates together and render the hemostatic plug resistant to degradation. Fibrin strand formation is the culmination of the coagulation pathway, which is initiated by tissue factor exposed to the blood when the vessel is injured. Thus, the connective tissue surrounding blood vessels, the adventitia, is rich in tissue factor. Damage to the outside of the vessel disrupts this hemostatic envelope and triggers a series of connected reactions that culminate in a burst of thrombin generation. Through limited proteolysis, thrombin converts soluble fibrinogen into fibrin monomers, which then polymerize to form the fibrin protofibrils that give thrombi their 3-dimensional structure. Thrombin also serves as a potent platelet agonist that recruits additional platelets into the platelet–fibrin thrombus. Therefore, platelet responsiveness to external stimuli and rapid generation of large amounts of thrombin are essential for effective hemostatic plug formation at sites of vascular injury.

The third and final line of defense at sites of vascular compromise involves the degradation of the hemostatic plug once it has served its barrier function. This pathway is initiated when tissue-type plasminogen activator released from the damaged vessel wall converts plasminogen to plasmin. Plasmin degrades the fibrin strands into soluble fragments, thereby dissolving the hemostatic plug and restoring the vessel to its native state. Therefore, integration of this fibrinolytic pathway with the processes involved in clot formation is essential for maintenance of vascular integrity.

Thrombosis occurs when a clot forms inside a vessel instead of where the vessel wall has been breached by injury. Thrombosis can occur in arteries or in veins. Arterial thrombosis is the underlying cause of most heart attacks and strokes, whereas venous thrombi in deep veins, the so-called deep vein thrombosis, can break off and travel to the lungs to produce a pulmonary embolism. Therefore, it is not surprising that tremendous efforts have been made to better understand the pathophysiology of thrombosis and to develop antiplatelet drugs and anticoagulants to prevent and treat this common and potentially life-threatening condition.

This supplement provides an overview of some of the innovations that have culminated in the development of new antithrombotic therapies. In addition, it describes emerging gene therapy approaches for the treatment of hemophilia; bleeding disorders caused by reduced thrombin generation as a result of congenital deficiency of factor VIII or factor IX. The supplement starts with the article by Wendelboe and Raskob who remind us that thromboembolism accounts for 1 in 4 deaths worldwide and remains the leading cause of mortality. Although the incidence has declined and mortality rates of thromboembolism have steadily decreased in established market economies, the global burden is increasing. This increase...
Thrombosis occurs when there is disruption of the dynamic balance between clot formation and clot dissolution. The interplay between these complex processes is amenable to mathematical and computational modeling and microfluidic lab-on-a-chip systems can be used to simulate the vasculature. Such systems have the potential to not only identify the factors that regulate the growth and morphology of clots but also evaluate drug therapies and the performance of stents and other cardiovascular devices. In his review, Diamond describes how several laboratories have used systems analysis to decompose the complex processes involved in thrombus formation and dissolution by integrating genotyping, high-dimensional phenotyping, biomarker surveillance, imaging, and other techniques. Aimed at gaining a better understanding of the molecular mechanisms that underpin thrombosis, the systems biology approach has the potential to inform and optimize thrombosis management.

Thrombus formation in arteries or veins involves interactions between platelets, leukocyte, and clotting proteins and the vessel wall. Even with advanced microfluidic systems, these complex interactions are impossible to simulate in vitro. The article by Jagadeeswaran et al highlights how zebrafish and animal models have provided insights into the pathogenesis of arterial and venous thrombosis. Mouse models of thrombosis have enabled the identification of potential new initiators of clotting, including inorganic polyphosphates, neutrophil extracellular traps, and procoagulant microparticles. Studies are now underway to determine the role of these initiators in humans. Thrombosis models in mice, rats, rabbits, and nonhuman primates have been used to support New Drug Applications for antithrombosis drugs. Mouse models of thrombosis can be used to rapidly screen compounds that interfere with clot formation, thereby preventing the synthesis of thromboxane A2, an agonist released from activated platelets. In contrast, clopidogrel attenuates platelet activation by irreversibly blocking P2Y12, the major ADP receptor on the platelet surface. With P2Y12 blocked, ADP released from activated platelets is unable to recruit ambient platelets to sites of injury.

Focusing on coronary artery disease, Gurbe et al describe how recently developed point-of-care tests have demonstrated variable response to clopidogrel in patients undergoing coronary artery stenting. Patients with high platelet reactivity, indicating incomplete ADP receptor blockade, seem to be at increased risk of thrombotic events, whereas those with low platelet reactivity, indicating nearly complete ADP receptor blockade, seem to be at increased risk of bleeding. These findings raise the possibility of precision inhibition of P2Y12.

Despite overwhelming evidence from observational studies that high platelet reactivity is associated with poorer clinical outcomes, randomized controlled trials have to date failed to show that the use of bedside testing to inform P2Y12 receptor antagonist dosing improves outcomes. However, additional trials are ongoing.

Thrombosis and inflammation are intimately linked. Patients with chronic inflammatory conditions are prone to thrombosis, and thrombosis is often associated with inflammation. Foley and Conway explain these phenomena and describe the cross talk between coagulation and inflammatory pathways and indicate how their integration optimizes the response to injury or pathogen invasion. Tissue factor and thrombin are important links between coagulation and inflammation, and both are critical components of innate immunity. Consequently, modulation of coagulation has the potential to modulate inflammation and vice versa. Future therapies can exploit this link.

Anticoagulants are not only the foundation of treatment of venous thrombosis but also are used for stroke prevention in patients with atrial fibrillation. The burden of venous thromboembolism and atrial fibrillation increases with age and with the aging population; these disorders are increasingly important healthcare concerns. Atrial fibrillation is particularly problematic because the life-time risk of this disorder is 25% in those over the age of 40 years and atrial fibrillation increases the risk of stroke by 5-fold. Furthermore, strokes in patients with atrial fibrillation are large, have higher mortality rates than strokes in those without this arrhythmia and in survivors, are more likely to lead to long-term disability. Therefore, more and more patients require lifelong anticoagulation therapy to prevent stroke and recurrent venous thromboembolism.

For >65 years, vitamin K antagonists, such as warfarin, were the only available oral anticoagulants. Chan et al describe how elucidation of the crystal structures of thrombin and factor Xa enabled structure-based design of small molecules that bind to the active site of these enzymes with high affinity and specificity. With predictable pharmacokinetic and pharmacodynamic responses, these direct oral inhibitors can be given in fixed doses without routine coagulation monitoring. Multiple randomized controlled trials have demonstrated that the direct oral anticoagulants are at least as effective and are safer than vitamin K antagonists for the prevention and
treatment of venous thromboembolism and for stroke prevention in patients with atrial fibrillation. By also simplifying anticoagulant therapy, the direct oral anticoagulants are rapidly replacing vitamin K antagonists for many indications and they have the potential to reduce the global burden of thrombosis. Nonetheless, unanswered questions remain. For example, more information is needed about the use of these agents in infants and children and about their efficacy and safety in patients with severe renal dysfunction or extremes of body weight. Ongoing trials are addressing these questions and are evaluating the utility of the direct oral anticoagulants for new indications, such as heart failure or secondary prevention in patients with coronary or peripheral artery disease.

After years of stagnation, recent advances in diagnosis and treatment are offering new hope for stroke patients. Hill et al.9 highlight the central role of brain imaging in defining management of acute ischemic stroke. Although intravenous thrombolytic therapy produces a clear benefit for patients presenting within 4.5 hours of onset of stroke symptoms, the introduction of thrombus extraction devices has provided the most dramatic advance. Endovascular approaches are rapidly becoming the new standard of care for the management of acute ischemic stroke, and these approaches extend the window for treatment from 4.5 hours to ≤8 hours. This extension offers more acute ischemic stroke patients an opportunity to benefit from potentially life-saving and disability-sparing treatment. Early initiation of antiplatelet therapy remains the foundation for secondary stroke prevention, and several randomized controlled trials are currently underway to evaluate whether different combinations of antiplatelet drugs or the direct oral anticoagulants produce greater reductions in recurrent stroke with an acceptable safety profile.

Moving from thrombosis to bleeding disorders, Swystun and Lillicrap10 remind us that insights into the genetics of the human coagulation system were among the first successes of the genetic revolution of the 1980s. Rapid advances in molecular genetics have informed current approaches to the diagnosis of many hemostatic and thrombotic disorders and have revolutionized the treatment of patients with hemophilia with the introduction of recombinant clotting proteins. Unfortunately, eliminating the risk of infection from plasma-derived clotting factors with recombinant factor VIII and factor IX came too late to save many patients who died from AIDS. Despite the promise, curative gene therapy for inherited disorders of coagulation remains elusive. Although continued improvements in the tools for effective and safe gene therapy suggest a bright future for genetic therapies of hemophilia, important obstacles remain.

Dramatic advances in our understanding of the mechanisms of thrombosis and hemostasis have transformed the management of thrombotic and bleeding disorders through the introduction of new, effective, safer, and more convenient therapies. Although much has been achieved, the reviews presented in this supplement highlight the unknowns and identify directions for future research.

Acknowledgements

J.I. Weitz holds the Canada Research Chair (Tier 1) in Thrombosis and the Heart and Stroke Foundation/J.F. Mustard Chair in Cardiovascular Research.

Disclosures

None.

References


Key Words: Editorials ■ anticoagulants ■ blood clotting ■ blood platelets ■ thrombosis ■ tissue plasminogen activator
Advances in Thrombosis and Hemostasis: An Introduction to the Compendium
Jeffrey I. Weitz and John W. Eikelboom

Circ Res. 2016;118:1337-1339
doi: 10.1161/CIRCRESAHA.116.308844

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/118/9/1337