Deep vein thrombosis and pulmonary embolism are collectively called venous thromboembolism (VTE) and are a major cause of morbidity and mortality in the United States and Europe. March is deep vein thrombosis awareness month in the United States, and each year Arteriosclerosis, Thrombosis, and Vascular Biology marks this event with a series of reviews on VTE. This year we have 3 excellent articles on (1) mouse models of venous thrombosis, (2) risk factors for VTE in humans, and (3) the new generation of oral anticoagulants that are available to treat VTE.

See accompanying articles on pages 556, 563, and 569

The first review, by Diaz et al describes how the use of mouse models has increased our understanding of the mechanisms of initiation, propagation, and resolution of venous clots. The obvious advantage of mice is that we can determine the effect of the loss or mutation of any given gene on thrombosis. Indeed, work with P-selectin knockout mice suggested a role for P-selectin in venous thrombosis that was subsequently confirmed in nonhuman primates. It will be interesting to see whether P-selectin inhibitors will be successfully developed as anticoagulant drugs. Mice have several disadvantages, however, including their small size, their resistance to thrombosis, and the surgical challenges of working with small vessels. Diaz et al evaluate 4 inferior vena cava (IVC) thrombosis models. The ferric chloride model induces oxidative damage to the vessel wall that produces an occlusive thrombosis. The advantage of this model is that it is reliable. However, the majority of clinical deep vein thrombosis cases are not associated with damage to the vessel wall. The IVC ligation model produces a reproducible thrombus that is ideal for studying thrombus resolution. Clot formation is likely to be triggered by tissue factor in the vessel wall and stasis. The disadvantages of this model are that the ligation damages the vessel wall and the absence of blood flow prevents the delivery of circulating procoagulant microparticles that may contribute to venous thrombosis. More recently, an IVC stenosis model of thrombosis has become popular because there is minimal damage to the endothelium and blood flow is maintained. Clot formation appears to be triggered by activation of the endothelium coupled with reduced blood flow. The disadvantage of this model is that many wild-type mice do not develop a thrombus, and there are large variations in thrombus size among mice that do develop thrombosis. Finally, the electrolytic IVC model activates the endothelium using an electric current. The advantages of this model are that it produces a reproducible thrombus that does not occlude the vessel, and blood flow is maintained. Unlike the IVC ligation stasis model, the thrombus grows in the direction of the blood flow. A disadvantage of this model is the longer operative time, need for addition equipment, and damage associated with insertion of the needle into the IVC.

An important issue with all the IVC thrombosis models is what to do with lateral and posterior side branches. Some studies ligate the lateral side branches to enhance clot formation whereas others do not. In addition, each mouse has a different vein anatomy that can contribute to the variation in clot formation. It would be helpful to standardize a mouse model of IVC thrombosis so that results from different laboratories can be compared. Future studies should also investigate venous thrombosis in different disease models and better define the role of circulating microparticles in thrombosis.

The review by Reitsma et al describes risk factors for VTE. It is likely that disturbed flow and stasis in the deepest parts of the valve pockets leads to endothelial cell activation and clot formation. Genetic risk factors for VTE include deficiencies in the anticoagulants antithrombin, protein C, and protein S; increased procoagulant potential associated with factor V Leiden, prothrombin G20210A, and the non-O blood group. Acquired risk factors for VTE include obesity, antiphospholipid syndrome, oral contraceptives and hormone replacement therapy, and pregnancy. New global assays of coagulation may be useful in identifying individuals at risk for VTE. The possible contributions of platelets, red blood cells, microparticles and neutrophil extracellular traps are discussed. Clearly, there is much to learn about the mechanisms that trigger venous thrombosis. It is hoped that physicians and the public will become more aware of the risk factors associated with VTE so that the number of events can be reduced.

There is good news about venous thrombosis treatment. Heparin and oral vitamin K antagonists have been used for more than 50 years for VTE treatment and prophylaxis. However, heparins must be administered parentally or intravenously and rely on the presence of antithrombin for inhibition. Vitamin K antagonists are oral drugs but are challenging to use because of the variability of dose response among patients and drug and diet interactions. Soff summaries...
rizes the plethora of clinical trials that have been performed on 3 new oral anticoagulant drugs, providing physicians with a new armament for the treatment of VTE. The 2 drugs approved by the US Food and Drug Administration are the factor Xa inhibitor rivaroxaban and the thrombin inhibitor dabigatran. They have 2 major advantages over heparins because they (1) are oral and (2) are direct inhibitors of factor Xa and thrombin. Importantly, a study of thromboprophylaxis in high-risk orthopedic patients found that rivaroxaban significantly reduced VTE compared with the low molecular weight heparin enoxaparin without increasing bleeding. This led to Food and Drug Administration approval of rivaroxaban in July 2011 for the prevention of VTE in patients undergoing knee and hip replacement surgery. Dabagatran was also shown to be noninferior to enoxaparin in 3 of 4 studies of VTE rates in total knee and total hip replacement surgery but has not been approved by the Food and Drug Administration. Rivaroxaban and dabigatran have both been compared with combined enoxaparin-vitamin K antagonist treatment of VTE. Rivaroxaban was noninferior to standard of care treatment with a same rate of bleeding. Similar results were observed with dabigatran. Despite these promising results the drugs have not yet been approved by the Food and Drug Administration for treatment of VTE. Finally, 2 studies have added the new factor Xa inhibitors to the standard antiplatelet agents to determine whether they can reduce cardiovascular event rates and death in acute coronary syndrome patients. Rivaroxaban reduced primary end points but increased bleeding, including intracranial hemorrhage. The study with the factor Xa inhibitor apixaban was stopped prematurely because of major bleeding in the apixaban group. These results suggest that the beneficial effects of factor Xa inhibition in acute coronary patients are offset by increased bleeding.

It will be interesting to see how rivaroxaban and dabigatran fare in the real world of patient care. Some limitations exist with the new oral anticoagulants that include a lack of assays for monitoring the intensity of anticoagulation and the absence of a reversal agent. PRT064445 has been developed by Portola Pharmaceuticals as a factor Xa inhibitor antidote and may be a key reversal agent for factor Xa inhibitors in the future. Nevertheless, the impressive clinical trial results suggest that the new generation of oral anticoagulant drugs will reduce the morbidity and mortality associated with VTE.

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References

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