presence of the *JAK2* V617F mutation. Therefore, prophylaxis with low-dose aspirin is probably justified in patients with high-risk essential thrombocythemia and other myeloproliferative disorders.

Increased platelet turnover in thrombocytosis is also associated with thromboembolic complications, but this does not necessarily involve high platelet counts, as has been demonstrated by radioactive platelet survival studies and an increase in reticulated (young) platelets in thrombotic essential thrombocytopenia. Moreover, successful treatment of symptomatic patients with aspirin increases platelet survival by decreasing platelet clearance. Concomitant therapy to prevent thrombotic complications of thrombocytosis includes lowering the platelet count with hydroxyurea. Evidence suggests that patients with essential thrombocythemia who are at high risk for arterial thrombosis are most effectively treated with the combination of hydroxyurea and low-dose aspirin. Patients with reactive (secondary) thrombocytosis resulting from iron deficiency anemia, chronic infection, rheumatoid arthritis, or the postsplenectomy state do not generally have increased thrombotic risk and do not require aspirin prophylaxis.

Heparin-Induced Thrombocytopenia

HIT must be distinguished from other drug-induced forms of immune thrombocytopenia because of its potentially catastrophic *thrombotic* complications and its unique pathophysiologic features. Almost 25% of patients who are exposed to UFH develop antibodies (detected by ELISA) that recognize the complex of heparin and platelet factor 4 (PF4), the latter being released from activated platelets. When such patients receive heparin again, between 5% and 10% develop HIT, most with platelet counts between 50,000 and 100,000/μL. HIT rarely occurs in patients who have not been previously exposed to heparin (0.3% incidence).

Surgery is a specific risk factor for HIT; the incidence of HIT in surgical patients is about 2.6%, compared with 1.7% in medical patients. HIT antibodies occur with high frequency in patients undergoing either cardiac surgery with cardiopulmonary bypass or an orthopedic procedure such as hip replacement. The incidence of HIT in patients who have received only LMWH is far lower, only about one-tenth the rate seen with UFH. However, the mechanism of thrombocytopenia for both UFH and LMWH appears to be similar: Platelet Fc-receptor binding of the heparin-PF4 antibody complex causes signal transduction and platelet activation with enhanced thrombin generation on the platelet surface.

The diagnosis is predominantly clinical (e.g., using the 4Ts algorithm for scoring HIT—magnitude of thrombocytopenia, timing of platelet fall, thrombotic sequelae, and ruling out other causes of thrombocytopenia), but the rapid ELISA test will detect heparin-PF4 antibodies in serum. The main drawback of ELISA is that it does not indicate whether the antibody complex is a functional activator of platelets; therefore, it is sensitive but not specific for HIT. The serotonin release assay is the functional test for HIT; it detects platelet activation after exposure to serum antibody in the presence of a therapeutic heparin level. However, a low probability for HIT based on the 4Ts score can be used to exclude the HIT diagnosis.

The thrombin-based procoagulant response in HIT incorporates platelets into microcirculatory clots, leading to thrombocytopenia; about 30% of HIT patients have overt thromboembolic complications, which can be severe or life-threatening. Thromboembolic events can occur before, concurrent with, and after development of thrombocytopenia in HIT, with about equal frequency. Although thrombosis is more frequent in patients with both HIT and concomitant cardiovascular disease and in those receiving full-dose heparin, any heparin dose (even heparin flushes) can result in thrombosis in HIT. Arterial and venous thromboembolic disease can occur even weeks after heparin has been discontinued, an effect perhaps mediated by EC glycosaminoglycan binding to PF4, which serves as a target for circulating HIT antibodies.

Discontinuation of all heparin is critical; moreover, although the antibody may have been induced by treatment with UFH, more than 80% of these antibodies cross-react with LMWH. Therefore, the preferred therapy for short-term anticoagulation in patients with HIT is a direct thrombin inhibitor (DTI), such as argatroban or bivalirudin, which is not a target for the heparin-PF4 antibodies. Indeed, because the event rate for subsequent thrombosis, limb amputation, and death is increased in patients with HIT even if they do not have thrombosis at presentation, DTI therapy is mandated after discontinuation of heparin. The choice of DTI may be dictated by other clinical conditions; for example, renal insufficiency slows bivalirudin clearance, increasing the bleeding risk, whereas argatroban is cleared by hepatic metabolism. For patients who develop HIT after warfarin has already been started, in addition to substituting a DTI, one should administer vitamin K to correct protein C levels. Although it has not been approved by the U.S. Food and Drug Administration (FDA) for this clinical scenario, the Xa inhibitor fondaparinux has the advantages of once-daily subcutaneous administration without need for laboratory monitoring and of having no affect on the international normalized ratio (INR).

DTI therapy should be continued until the platelet count is higher than 100-150,000/μL. Warfarin can then be added, and the two therapies should overlap for at least 5 days and with the INR at a therapeutic level for at least 48 hours. Because DTIs prolong the INR, a therapeutic warfarin level after 5 days may result in a supratherapeutic INR (usually >4); gradual downward titration of the DTI as the INR increases is a logical management strategy. Once DTIs are stopped, it is essential to repeat the INR measurement after 4 to 6 hours to confirm that it remains within the therapeutic range.

If there is no thrombosis with HIT, the total duration of anticoagulation should be 4 weeks; if thrombosis is present, anticoagulation should be continued for 3 to 6 months. Warfarin should never be used primarily to treat HIT, and it should not be instituted without simultaneous DTI coverage because it may induce acquired protein C deficiency leading to venous limb gangrene. One hallmark of protein C depletion in HIT is a sudden rise in the INR (to >3.5) after a single warfarin dose; in that circumstance, warfarin should be discontinued and the patient repleted with vitamin K. Patients with a history of HIT who need surgery requiring cardiopulmonary bypass can be safely reexposed to brief systemic UFH if ELISA testing is negative for the antibody at least 100 days after the previous UFH exposure.