TABLE 52-4 LABORATORY EVALUATION OF VENOUS THROMBOSIS

Activated protein C resistance, factor V Leiden	Prothrombin G20210A mutation
Lupus anticoagulant	Antithrombin activity
Anticardiolipin, anti–β_2-glycoprotein I antibody serology	Protein C activity
Homocysteine level: fasting or after methionine load	Free protein S level

patient is heterozygous or homozygous, although it may miss rare variants of APC resistance.

The utility of laboratory testing in the setting of atherothrombosis and arterial thromboembolism is unclear. In the setting of a myeloproliferative disorder, the platelet count and platelet function (e.g., aggregation and closure times) can justify hydroxyurea and/or aspirin therapy. In patients with unusual or recurrent arterial disease, other assays can be justified, including testing for t-PA and PAI-1 levels and for dysfibrinogenemia (thrombin time and antigen : activity ratio), all of which should be performed in consultation with specialists in hemostasis.

THERAPY FOR VENOUS THROMBOEMBOLISM

Once VTE has been diagnosed, immediate therapy is required. In most patients, anticoagulation is accomplished on a short-term basis with heparin compounds and on a long-term basis with warfarin. Thrombolytic therapy is indicated for patients with extensive proximal venous clots or PE. IVC filters are used in patients with contraindications to anticoagulation, complications of anticoagulation (usually active bleeding), or failure of anticoagulation (recurrent PE). IVC filters clearly decrease the incidence of early PE, but their use is also associated with thrombosis at the insertion site and late complications of IVC thrombosis as well as a 10% to 20% incidence of postphlebitic syndrome. Temporary IVC filters are often used in trauma patients and appear to be most efficacious when they are placed for fewer than 7 to 10 days.

UFH is often the anticoagulation therapy of choice for inpatients because of its short half-life and reversibility, but LMWH is increasingly used for this indication. UFH is begun as a bolus intravenous infusion of 80 U/kg, followed by a continuous infusion of 18 U/kg/hour; UFH doses in excess of 30,000 U/day have been shown to be most efficacious at preventing recurrent VTE. UFH is monitored by the PTT, and the therapeutic PTT range determined by each hospital corresponds to anti-Xa levels of 0.3 to 0.7 U/mL. All hospitals have established protocols for adjustment of UFH infusion based on the patient's weight and PTT monitoring.

UFH should be continued for at least 4 days (longer in patients with extensive clots) and may be discontinued after the patient has been fully anticoagulated with warfarin (INR ≥2 for 2 consecutive days). Some patients receiving large doses of heparin (usually >40,000 U/day) do not develop a therapeutic PTT. This *heparin resistance* can be caused by a variety of mechanisms, including increased heparin-binding proteins, counteracting medications (e.g., protamine), and decreased AT. An *apparent* heparin resistance is often seen in patients with coexistent inflammatory disease with high plasma levels of factor VIII and fibrinogen; direct monitoring of anti-Xa levels is indicated.

LMWH is an excellent alternative to UFH in the treatment of thromboembolism and acute coronary events. The small controlled-size elements of LMWH stimulate AT activity that is more restricted to factor Xa compared with UFH, which has effects on thrombin, factor IX, and factor XI, in addition to others. The practical advantages of LMWH over UFH include increased plasma half-life, more predictable dose response allowing for intermittent fixed dosing, a lower de novo incidence of HIT (10% to 20% of the rate for UFH), and significantly reduced monitoring requirements. LMWH levels are prolonged in renal failure and in those circumstances may need to be monitored and adjusted based on anti-Xa levels. Peak anti-Xa levels (0.5 to 1 U/mL for twice-daily dosing and 1 to 2 U/mL for once-daily dosing) typically occur between 3 and 5 hours after subcutaneous LMWH injection. As with UFH, switching from LMWH to warfarin for long-term management can be accomplished after therapeutic INR values have been present for at least 2 days.

Warfarin and LMWH are used for long-term prophylaxis of VTE. Warfarin should be begun during the first 24 hours after presentation with VTE, concurrent with heparin treatment. The PT is prolonged within hours by warfarin because of a rapid decrease in factor VII levels; however, therapeutic warfarin anticoagulation does not occur until other vitamin K–dependent factors (II, IX, and X) also decrease. Therapeutic warfarin anticoagulation is usually achieved within 4 to 5 days with adequate warfarin dosing; UFH or LMWH may be discontinued after the INR has been greater than 2 for at least 2 consecutive days. One long-standing problem with warfarin anticoagulation is the interindividual variability in INR response; at least 50% of this variability in sensitivity to warfarin may be explained by polymorphisms in the *CYP2C9* and *VKORC1* genes. Although these have been incorporated into models for predicting safe and therapeutic warfarin dosing, most clinicians simply begin dosing and adjust therapy as needed based on periodic monitoring.

The therapeutic INR range depends on the condition predisposing the patient to thromboembolism. Prophylaxis after uncomplicated VTE in a patient without known risk factors requires an INR between 2 and 3; in contrast, warfarin prophylaxis for patients with APS and recurrent VTE may require INR values between 3 and 4 (Table 52-5).

The duration of warfarin or LMWH prophylaxis varies depending on the circumstances of the VTE, the risk for bleeding, and the potential for recurrence. In general, the longer the period of anticoagulation with warfarin, the less the chance of recurrence. Short-term warfarin (6 weeks) is less effective at preventing recurrence that longer courses (6 months). Patients with definite transient risk factors such as orthopedic surgery have low recurrence rates, even with short-term therapy; still, prolonged thromboprophylaxis (>21 days) after total hip replacement is more efficacious than shorter therapy (7 to 10 days). It is not clear that oral Xa inhibitors and dabigatran provide any benefit over LMWH for thromboprophylaxis after total hip or knee replacement (Table 52-6).

In contrast, patients with "unprovoked" VTE (i.e., outside the setting of trauma, surgery, immobilization, pregnancy, or cancer) have significant recurrence rates, even after 3 to 6 months of