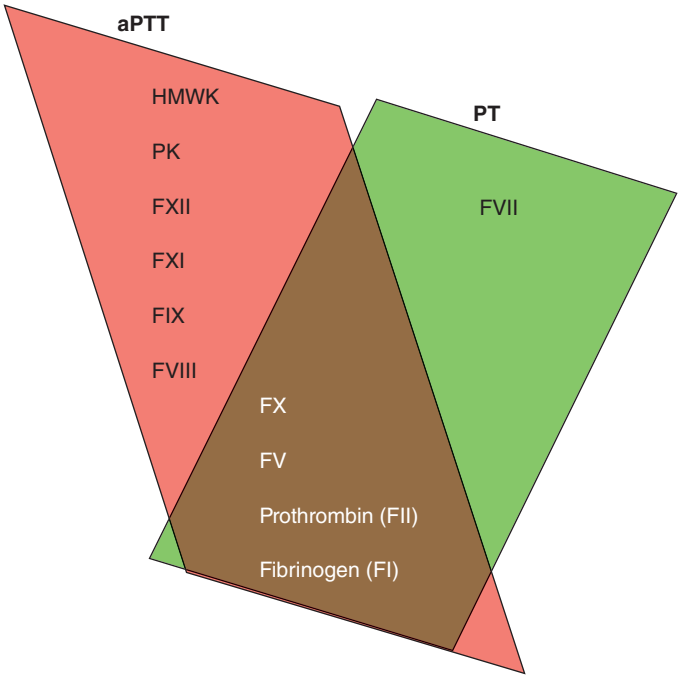

FIGURE 78–6 **Coagulation factor activity** tested in the activated partial thromboplastin time (aPTT) in red and prothrombin time (PT) in green, or both. F, factor; HMWK, high-molecular-weight kininogen; PK, prekallikrein.

TABLE 78-4 HEMOSTATIC DISORDERS AND COAGULATION TEST ABNORMALITIES

Prolonged Activated Partial Thromboplastin Time (aPTT)
No clinical bleeding—↓ factor XII, high-molecular-weight kininogen, prekallikrein
Variable, but usually mild, bleeding—↓ factor XI, mild ↓ factor VIII and factor IX
Frequent, severe bleeding—severe deficiencies of factors VIII and IX
Heparin and direct thrombin inhibitors
Prolonged Prothrombin Time (PT)
Factor VII deficiency
Vitamin K deficiency—early
Warfarin anticoagulation
Direct Xa inhibitors (rivaroxaban, apixaban)
Prolonged aPTT and PT
Factor II, V, X, or fibrinogen deficiency
Vitamin K deficiency—late
Direct thrombin inhibitors
Prolonged Thrombin Time
Heparin or heparin-like inhibitors
Direct thrombin inhibitors (e.g., dabigatran, argatroban, bivalirudin)
Mild or no bleeding—dysfibrinogenemia
Frequent, severe bleeding—afibrinogenemia
Prolonged PT and/or aPTT Not Corrected with Mixing with Normal Plasma
Bleeding—specific factor inhibitor
No symptoms, or clotting and/or pregnancy loss—lupus anticoagulant
Disseminated intravascular coagulation
Heparin or direct thrombin inhibitor
Abnormal Clot Solubility
Factor XIII deficiency
Inhibitors or defective cross-linking
Rapid Clot Lysis
Deficiency of α_2-antiplasmin or plasminogen activator inhibitor 1
Treatment with fibrinolytic therapy

high-molecular-weight kininogen; and factor XII (Fig. 78-6). The aPTT reagent contains phospholipids derived from either animal or vegetable sources that function as a platelet substitute in the coagulation pathways and includes an activator of the intrinsic coagulation system, such as nonparticulate ellagic acid or the particulate activators kaolin, celite, or micronized silica.

The phospholipid composition of aPTT reagents varies, which influences the sensitivity of individual reagents to clotting factor deficiencies and to inhibitors such as heparin and lupus anticoagulants. Thus, aPTT results will vary from one laboratory to another, and the normal range in the laboratory where the testing occurs should be used in the interpretation. Local laboratories can relate their aPTT values to the therapeutic heparin anticoagulation by correlating aPTT values with direct measurements of heparin activity (anti-Xa or protamine titration assays) in samples from heparinized patients, although correlation between these assays is often poor. The aPTT reagent will vary in sensitivity to individual factor deficiencies and usually becomes prolonged with individual factor deficiencies of 30–50%.

Mixing Studies Mixing studies are used to evaluate a prolonged aPTT or, less commonly PT, to distinguish between a factor deficiency and an inhibitor. In this assay, normal plasma and patient plasma are mixed in a 1:1 ratio, and the aPTT or PT is determined immediately and after incubation at 37°C for varying times, typically 30, 60, and/or 120 min. With isolated factor deficiencies, the aPTT will correct with mixing and stay corrected with incubation. With aPTT prolongation due to a lupus anticoagulant, the mixing and incubation will show no correction. In acquired neutralizing factor antibodies, notably an acquired factor VIII inhibitor, the initial assay may or may not correct immediately after mixing but will prolong or remain prolonged with incubation at 37°C. Failure to correct with mixing can also be due to the presence of other inhibitors or interfering substances such as heparin, fibrin split products, and paraproteins.

Specific Factor Assays Decisions to proceed with specific clotting factor assays will be influenced by the clinical situation and the results of coagulation screening tests. Precise diagnosis and effective management of inherited and acquired coagulation deficiencies necessitate quantitation of the relevant factors. When bleeding is severe, specific assays are urgently required to guide appropriate therapy. Individual factor assays are usually performed as modifications of the mixing study, where the patient's plasma is mixed with plasma deficient in the factor being studied. This will correct all factor deficiencies to >50%, thus making prolongation of clot formation due to a factor deficiency dependent on the factor missing from the added plasma.

Testing for Antiphospholipid Antibodies Antibodies to phospholipids (cardiolipin) or phospholipid-binding proteins (β_2-microglobulin and others) are detected by enzyme-linked immunosorbent assay (ELISA). When these antibodies interfere with phospholipid-dependent coagulation tests, they are termed *lupus anticoagulants*. The aPTT has variability sensitivity to lupus anticoagulants, depending in part on the aPTT reagents used. An assay using a sensitive reagent has been termed an *LA-PTT*. The dilute Russell viper venom test (dRVVT) and the tissue thromboplastin inhibition (TTI) test are modifications of standard tests with the phospholipid reagent decreased, thus increasing the sensitivity to antibodies that interfere with the phospholipid component. The tests, however, are not specific for lupus anticoagulants, because factor deficiencies or other inhibitors will also result in prolongation. Documentation of a lupus anticoagulant requires not only prolongation of a phospholipid-dependent coagulation test but also lack of correction when mixed with normal plasma and correction with the addition of activated platelet membranes or certain phospholipids (e.g., hexagonal phase).