TABLE 300-3 ANTICOAGULATION OF VTE

Immediate Anticoagulation
Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, *or*
Enoxaparin 1 mg/kg twice daily with normal renal function, *or*
Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, *or*
Tinzaparin 175 U/kg once daily with normal renal function, *or*
Fondaparinux weight-based once daily; adjust for impaired renal function
Direct thrombin inhibitors: argatroban or bivalirudin
Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter
Apixaban (not yet licensed)
Warfarin Anticoagulation
Requires 5–10 days of administration to achieve effectiveness as monotherapy
(Unfractionated heparin, low-molecular-weight heparin, and fondaparinux are the usual immediately effective "bridging agents" used when initiating warfarin)
Usual start dose is 5 mg
Titrate to INR, target 2.0–3.0
Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range
Novel Oral Anticoagulants for Extended-Duration Anticoagulation following Initial Parenteral Anticoagulation
Edoxaban (not yet licensed)
Dabigatran (not yet licensed)

of parenteral therapy "bridged" to warfarin, (2) parenteral therapy "bridged" to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation with rivaroxaban or apixaban (both are anti-Xa agents) with a loading dose followed by a maintenance dose as monotherapy without parenteral anticoagulation.

The three heparin-based parenteral anticoagulants are (1) unfractionated heparin (UFH), (2) low-molecular-weight heparin (LMWH), and (3) fondaparinux. For patients with suspected or proven heparin-induced thrombocytopenia, there are two parenteral direct thrombin inhibitors: argatroban and bivalirudin **(Table 300-3)**.

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h.

The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired.

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

WARFARIN DOSING In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin **(Chap. 78)**. The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. *CYP2C9* variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K epoxide reductase complex 1 (*VKORC1*) can predict whether patients require low, moderate, or high warfarin doses.

Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin.

Novel Oral Anticoagulants Novel oral anticoagulants are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions that make warfarin so difficult to dose. Rivaroxaban, a factor Xa inhibitor, is approved for treatment of acute DVT and acute PE as monotherapy, without a parenteral "bridging" anticoagulant. Apixaban is likely to receive similar approval for oral monotherapy. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are likely to be approved for treatment of VTE after an initial course of parenteral anticoagulation.

Complications of Anticoagulants The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. Heparin-induced thrombocytopenia is less common with LMWH than with UFH. There is no specific reversal agent for bleeding caused by fondaparinux, direct thrombin inhibitors, or factor Xa inhibitors.

Major bleeding from warfarin is best managed with prothrombin complex concentrate. With serious but non–life-threatening bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Recombinant human coagulation factor VIIa (rFVIIa) is an off-label option to manage catastrophic bleeding from warfarin, but prothrombin complex concentrate is a better choice. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

Duration of Anticoagulation For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation usually suffice. For an initial episode of provoked proximal leg DVT or PE, 3 to 6 months of anticoagulation are considered sufficient. For patients with cancer and VTE, prescribe LMWH as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering