TABLE 52-5 THERAPEUTIC INTERNATIONAL NORMALIZED RATIO (INR) RANGES FOR WARFARIN

PATIENT SUBGROUP	INR RANGE
VENOUS THROMBOSIS	
Treatment	2.0-3.0
Prophylaxis	1.5-2.5
ARTIFICIAL HEART VALVES	
Tissue	2.0-2.5
Mechanical	3.0-4.0
ATRIAL FIBRILLATION (NONVALVULAR)	
Prophylaxis	1.5-2.5
LUPUS ANTICOAGULANT	
Treatment, prophylaxis	2.0-3.0
Refractory thromboembolism	3.0-4.0

TABLE 52-6 NEW ORAL ANTICOAGULANTS (NOAC) AND THEIR INDICATIONS

NOAC	INDICATIONS
Dabigatran	Direct thrombin inhibitor for nonvalvular atrial fibrillation (to prevent stroke and non-CNS embolism)
Rivaroxaban	Anti-Xa for nonvalvular atrial fibrillation (to prevent stroke and non-CNS embolism); treatment of VTE and subsequent prophylaxis; and prophylaxis of VTE after hip or knee replacement
Apixaban	Anti-Xa for nonvalvular atrial fibrillation (to prevent stroke and non-CNS embolism)
Edoxaban	Anti-Xa for prevention of VTE in surgical patients; prevention of embolism in atrial fibrillation
Ticagrelor	Platelet P2RY12 inhibitor for prevention of thrombosis in acute coronary syndromes

CNS, Central nervous system; VTE, venous thromboembolism; Xa, activated factor X.

TABLE 52-7 GUIDELINES FOR DURATION OF PROPHYLACTIC ANTICOAGULATION AFTER VTE

CONDITION	DURATION OF THERAPY
Distal or superficial vein thrombus	3-12 wk
FIRST PROXIMAL VTE	
No risk factors	3-6 mo*
Correctable risk factor (e.g., surgery, trauma)	3-6 mo
Malignancy	Long-term†
Antiphospholipid syndrome	Long-term
Inherited risk factor‡	>6 mo
Recurrent VTE/PE	Lifelong

PE, Pulmonary embolism; VTE, venous thromboembolism (includes deep vein thrombosis, pulmonary embolism, and sinus or cerebral thrombosis).

*Evaluation of D-dimer after 3-6 mo may assist in the decision to stop prophylaxis.

†Long-term therapy must be adjusted individually according to presence of other diseases, risks for bleeding, presence of transient risk factors, and ease of compliance.

‡Inherited risk factors include factor V Leiden; prothrombin 20210A; deficiencies of antithrombin, protein C, or protein S.

TABLE 52-8 DRUGS THAT AFFECT WARFARIN LEVELS

INCREASED WARFARIN LEVELS: PROLONGED INR	DECREASED WARFARIN LEVELS: SUBTHERAPEUTIC INR
↓ Warfarin clearance	↑ Hepatic metabolism of warfarin
Disulfiram	Barbiturates
Metronidazole	Rifampin
Trimethoprim-sulfamethoxazole	↓ Warfarin absorption
↓ Warfarin-protein binding	Cholestyramine
Phenylbutazone	
↑ Vitamin K turnover	
Clofibrate	

↑, Increased; ↓, decreased; INR, international normalized ratio.

warfarin therapy. Because the risk for recurrence in patients with unprovoked proximal VTE or PE is relatively low when D-dimer levels are normal 3 weeks after cessation of anticoagulation, this measure may help providers decide whether anticoagulation past 3 to 6 months is necessary.

Evidence also indicates that inherited hypercoagulable disorders (e.g., FVL) probably confer a lifelong increased risk for VTE or PE. Some studies have shown that the bleeding risks incurred by long-term, low-intensity warfarin use are favorably balanced by the decreased incidence of recurrent thrombosis. Therefore, the presence of inherited thrombophilia may warrant continuation of warfarin therapy for a longer period, depending on the patient's other medical illnesses and whether transient circumstances may have predisposed the patient to VTE. Patients who develop recurrent VTE after discontinuation of warfarin should receive long-term anticoagulation regardless of whether they have a defined cause of thrombophilia. Patients with APS and a first episode of VTE are at very high risk for recurrent VTE (up to 50% per year) after anticoagulation is discontinued, clearly supporting the rationale of testing for antiphospholipid. Table 52-7 suggests broad guidelines for the duration of warfarin therapy in specific patient subgroups. Because warfarin is a teratogen, effective contraception should be used concurrently in women of childbearing age.

Supratherapeutic INR levels commonly occur with warfarin therapy, with or without bleeding. In patients with moderately elevated INR values (>5) and little or no bleeding, temporary discontinuation of warfarin and reinstitution of the drug at a lower maintenance dose may be sufficient. Patients with higher INR values (5 to 9) who are without serious bleeding should have warfarin withheld and should receive low doses (1 to 2.5 mg/day) of oral vitamin K to reach therapeutic INR levels; parenteral vitamin K may be given if gastrointestinal function is problematic. If serious active bleeding occurs with high INR values, especially if surgery is required to correct the bleeding, a combination of vitamin K and transfusion of plasma (see Chapter 51) will rapidly correct the INR. The INR can become elevated as a result of concurrent use of drugs that increase free warfarin levels (Table 52-8). Whenever bleeding occurs as a complication of anticoagulation, serious consideration must be given to future bleeding risks and to whether the patient requires placement of an IVC filter for prophylaxis.

Antithrombotic Therapy during Pregnancy

Heparins, both UFH and LMWH, are the safest therapy for venous thrombosis during pregnancy. Heparin does not cross the placenta, unlike warfarin, which causes a characteristic fetal embryopathy. Warfarin also causes fetal hemorrhage and placental abruption and should be avoided during pregnancy. VTE or PE during pregnancy should be treated with intravenous UFH for 5 to 10 days, followed by an adjusted-dose regimen of subcutaneous UFH, starting with 20,000 U every 12 hours and adjusted to achieve a PTT higher than 1.5 times baseline at 6 hours after