TABLE 143-8 FREQUENCIES OF *CYP2C9* GENOTYPES AND *VKORC1* HAPLOTYPES IN DIFFERENT POPULATIONS AND THEIR EFFECT ON WARFARIN DOSE REQUIREMENTS

Genotype/Haplotype	Frequency, %			Dose Reduction Compared with Wild-Type
	Caucasians	African Americans (A/A)	Asians (A)	
CYP2C9				
*1/*1	70	90	95	–
*1/*2	17	2	0	22
*1/*3	9	3	4	34
*2/*2	2	0	0	43
*2/*3	1	0	0	53
*3/*3	0	0	1	76
VKORC1				
Non-A/non-A	37	82	7	–
Non-A/A	45	12	30	26
A/A	18	6	63	50

gastrointestinal tract. Levels of warfarin in the blood peak about 90 min after drug administration. Racemic warfarin has a plasma half-life of 36–42 h, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.

Warfarin accumulates in the liver where the two isomers are metabolized via distinct pathways. *CYP2C9* mediates oxidative metabolism of the more active S isomer (Fig. 143-6). Two relatively common variants, *CYP2C9*2* and *CYP2C9*3*, encode an enzyme with reduced activity. Patients with these variants require lower maintenance doses of warfarin. Approximately 25% of Caucasians have at least one variant allele of *CYP2C9*2* or *CYP2C9*3*, whereas those variant alleles are less common in African Americans and Asians (Table 143-8). Heterozygosity for *CYP2C9*2* or *CYP2C9*3* decreases the warfarin dose requirement by 20–30% relative to that required in subjects with the wild-type *CYP2C9*1/*1* alleles, whereas homozygosity for the *CYP2C9*2* or *CYP2C9*3* alleles reduces the warfarin dose requirement by 50–70%.

Consistent with their decreased warfarin dose requirement, subjects with at least one *CYP2C9* variant allele are at increased risk for bleeding. Compared with individuals with no variant alleles, the relative risks for warfarin-associated bleeding in *CYP2C9*2* or *CYP2C9*3* carriers are 1.9 and 1.8, respectively.

Polymorphisms in *VKORC1* also can influence the anticoagulant response to warfarin. Several genetic variations of *VKORC1* are in strong linkage disequilibrium and have been designated as non-A haplotypes. *VKORC1* variants are more prevalent than variants of *CYP2C9*. Asians have the highest prevalence of *VKORC1* variants, followed by Caucasians and African Americans (Table 143-8). Polymorphisms in *VKORC1* likely explain 30% of the variability in warfarin dose requirements. Compared with *VKORC1* non-A/non-A homozygotes, the warfarin dose requirement decreases by 25 and 50% in A haplotype heterozygotes and homozygotes, respectively. These findings prompted the Food and Drug Administration to amend the prescribing information for warfarin to indicate that lower initiation doses should be considered for patients with *CYP2C9* and *VKORC1* genetic variants. In addition to genotype data, other pertinent patient information has been incorporated into warfarin dosing algorithms. Although such algorithms help predict suitable warfarin doses, it remains unclear whether better dose identification improves patient outcome in terms of reducing hemorrhagic complications or recurrent thrombotic events.

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter absorption, clearance, or metabolism of warfarin. Because of the variability in the anticoagulant response to warfarin, coagulation monitoring is essential to ensure that a therapeutic response is obtained.

MONITORING Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII, and factor X. The test is performed by adding thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determining the time to clot formation. Thromboplastins vary in their sensitivity to reductions in the levels of the vitamin K–dependent clotting factors. Thus, less sensitive thromboplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. This is problematic because higher doses of warfarin increase the risk of bleeding.

The INR was developed to circumvent many of the problems associated with the prothrombin time. To calculate the INR, the patient's prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), which is an index of the sensitivity of the thromboplastin used for prothrombin time determination to reductions in the levels of the vitamin K–dependent clotting factors. Highly sensitive thromboplastins have an ISI of 1.0. Most current thromboplastins have ISI values that range from 1.0 to 1.4.

Although the INR has helped to standardize anticoagulant practice, problems persist. The precision of INR determination varies depending on reagent-coagulometer combinations. This leads to variability in the INR results. Also complicating INR determination is unreliable reporting of the ISI by thromboplastin manufacturers. Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers using the same coagulometer that is used for patient samples.

For most indications, warfarin is administered in doses that produce a target INR of 2.0–3.0. An exception is patients with mechanical heart valves, particularly those in the mitral position or older ball and cage valves in the aortic position, where a target INR of 2.5–3.5 is recommended. Studies in atrial fibrillation demonstrate an increased risk of cardioembolic stroke when the INR falls to <1.7 and an increase in bleeding with INR values >4.5. These findings highlight the fact that vitamin K antagonists have a narrow therapeutic window. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked venous thromboembolism demonstrated a higher rate of recurrent venous thromboembolism with a target INR of 1.5–1.9 compared with a target INR of 2.0–3.0.

DOSING Warfarin is usually started at a dose of 5–10 mg. Lower doses are used for patients with *CYP2C9* or *VKORC1* polymorphisms, which affect the pharmacodynamics or pharmacokinetics of warfarin and render patients more sensitive to the drug. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant initial treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Early prolongation of the INR reflects reduction in the functional levels of factor VII. Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of factor Xa and prothrombin have been reduced into the therapeutic range with warfarin.

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is maintained. Even patients with stable warfarin dose requirements should have their INR determined every 3–4 weeks. More frequent monitoring is necessary when new medications are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin.