Warfarin is the most widely used oral anticoagulant for the treatment of thromboembolic disorders and for stroke prophylaxis. Warfarin is a problematic drug because it exhibits large interindividual variation in the required therapeutic dose, has a narrow therapeutic range, and shows multiple food and drug interactions. Its anticoagulant effect is monitored by measuring the international normalized ratio (INR), which is a function of the ratio of the time required for a patient’s blood to coagulate relative to that of a reference blood sample. Although warfarin has been used in humans for more than 50 years, its main side effect—bleeding—is a leading cause of hospital admission and drug-related death (1, 2). This problem has made patients and clinicians yearn for a new efficient and safe oral anticoagulant drug that does not require frequent monitoring. In Europe, a new oral anticoagulant drug (dabigatran) claimed to have these qualities has been licensed for short-term primary prevention of venous thromboembolic events, but its effectiveness in long-term secondary thromboprophylaxis remains to be shown. Furthermore, the daily cost of dabigatran is 5 times that of warfarin therapy including INR tests. To switch all warfarin patients (currently 1% of the population in many Western countries) to dabigatran would boost national costs in countries with subsidized drug programs; therefore, national authorities will probably endorse doses have been developed. These algorithms combine genetic, clinical, and demographic factors with warfarin-dosing data and INR measurements to estimate the probability that a patient’s INR will be within the tight therapeutic range. The required maintenance warfarin dose, which can vary 20-fold among individuals, can be roughly estimated from clinical and demographic factors, such as age, compliance, body weight, concurrent disease, and drug and food interactions (3). A number of dosage algorithms that use clinical and demographic factors have been tested and are able to reduce both the time to therapeutic anticoagulation and the frequency of INR monitoring (4). More recent discoveries have shown that variation in the genes that encode the main enzyme responsible for 3-warfarin metabolism (CYP2C9, cytochrome P450, family 2, subfamily C, polypeptide 9) and the target of warfarin in the vitamin K cycle (VKORC1, vitamin K epoxide reductase complex, subunit 1) influence dose requirements by affecting pharmacokinetics and pharmacodynamics (5). Polymorphisms in these genes are also associated with the risk of over-anticoagulation and bleeding during initiation of warfarin therapy (6). A large prospective study on warfarin pharmacogenetics provided probabilities of over-anticoagulation (INR >4) in patients with different CYP2C9 and VKORC1 alleles (Fig. 1) (7). During the first month of treatment, CYP2C9*3/*3 individuals had a 22-fold increased risk of an INR >4 and a tendency for more episodes of serious bleeding compared with individuals with other genotypes. Patients homozygous for VKORC1 variants had a 4.5-fold increased risk of an INR >4 within 5 weeks (7). Genotyping the CYP2C9 and VKORC1 genes could avoid overdosing in patients who have warfarin sensitivity caused by these polymorphisms. Several pharmacogenetic algorithms that predict warfarin maintenance doses have been developed. These algorithms combine genetic, clinical, and demographic factors with warfarin-dosing data and INR measurements to estimate the probability that a patient’s INR will be within the tight therapeutic range.

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2 Human genes: CYP2C9, cytochrome P450, family 2, subfamily C, polypeptide 9; VKORC1, vitamin K epoxide reductase complex, subunit 1.
In 2006, the AEI-Brookings Joint Center for Regulatory Studies estimated that American warfarin users would annually avoid 85,000 serious bleeding events and 17,000 strokes if genetic testing were integrated into routine warfarin therapy (8). According to the authors' calculations, genetic testing could reduce US healthcare spending by $1.1 billion per year, with a range of approximately $100 million to $2 billion. Even though these calculations might have been overly optimistic, an American regulatory agency, the Food and Drug Administration, decided to update the label of warfarin in August 2007 to encourage lower initiation doses in patients with CYP2C9 and VKORC1 variant alleles.

Warfarin has the potential to become one of the first drugs in which pharmacogenetic dosing is introduced into routine therapy; however, a few issues need to be resolved first. Pharmacogenetic dosing algorithms need to be adapted by including additional factors so that more ethnic groups can be analyzed. These algorithms currently predict approximately 50% of the dose variance in Caucasians; however, these algorithms perform less well in Asians and African Americans because of genetic homogeneity in the former and genetic diversity in the latter. Furthermore, existing pharmacogenetic algorithms show a poor fit at very high doses because they rely on genetic polymorphisms that increase the sensitivity to warfarin. This situation could be improved by incorporating into the dose models rarer mutations that cause warfarin resistance. Another question to be considered is how to predict loading doses from maintenance-dose models. Lastly, it is necessary to test the clinical utility of pharmacogenetic warfarin dosing before its implementation on a broad scale. Two prospective clinical
trials of predicted warfarin dosing have shown promising results (9, 10). In the trial of Caraco et al., 95 patients who began warfarin therapy according to their CYP2C9 genotype were compared with 96 patients who received their doses according to a clinical algorithm (9). In the clinical trial of Anderson et al., 101 patients who received their initial warfarin treatment according to their CYP2C9 and VKORC1 genotypes were compared with 99 patients randomized to standard therapy (10). Despite small sample sizes, both studies claimed that pharmacogenetics increased the efficiency of warfarin initiation. To produce irrefutable results, however, requires adequately powered randomized clinical trials of pharmacogenetic warfarin dosing. Two large clinical trials—one American and one European—of pharmacogenetic vs conventional warfarin initiation are starting in 2009. If the results from these large clinical trials are encouraging—and previous studies on warfarin pharmacogenetics suggest that they will be—then pharmacogenetic dosing will be ready to be introduced into clinical practice. It is hoped that the implementation of pharmacogenetics will improve the safety and cost-effectiveness of oral anticoagulant treatment. The long era of warfarin treatment as a leading cause of serious hospital admission and drug-related death could thereby be brought to an end.

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