



## Pharmacogenomic Testing and Warfarin Management

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**W**arfarin has been used for the prevention of thrombosis for more than 50 years and is the most frequently prescribed vitamin K antagonist in North America (Gage & Eby, 2003). Its mode of action is to prevent vitamin K from converting to vitamin KH<sub>2</sub>, thereby inhibiting clotting factors (Johnson & Cavallari, 2015). Warfarin metabolism is affected by variations in the cytochrome P450 2C9 (CYP2C9) and the vitamin K epoxide reductase complex 1 (VKORC1) genotypes. CYP2C9 affects the drug's pharmacokinetics, or metabolism, whereas VKORC1, the target protein of warfarin, affects the drug's pharmacodynamics, or its impact on cell proteins.

CYP2C9 variations can influence the dosage requirements of warfarin (Johnson & Cavallari, 2015). Most variations are caused by single nucleotide polymorphisms (SNPs) that lead to lower dosage requirements, with the exception of the CYP2C9\*6 allele, which is a single nucleotide deletion. Individuals who are homozygous for the wild type allele CYP2C9\*1 will typically have normal metabolism of warfarin. Individuals with one of the abnormal SNPs (i.e., either CYP2C9\*2 or CYP2C9\*3) metabolize warfarin more slowly and are prone to higher international normalized ratios (INRs) during the induction of warfarin therapy. These individuals are also about 2.6 times more prone to hemorrhage during the initiation of therapy than individuals with the normal allele (Gage & Eby, 2003). These two SNPs are the primary variations found in those of European descent and are found less often in people of African descent (Johnson & Cavallari, 2015). Other SNPs of CYP2C9 occur most often in people of African descent, and the presence of the CYP2C9\*2 allele is rare in those of Asian descent.

In addition, the presence of the single polymorphism A allele of VKORC1 is

associated with lower dosage requirements for warfarin and a higher risk of hemorrhage. The abnormal A allele is most commonly found in Asians followed by Europeans, and is least frequently seen in people of African descent. The impact of the VKORC1 abnormal allele on the risk of hemorrhage is apparent only in the first month of therapy; however, the presence of the CYP2C9\*2 and CYP2C9\*3 alleles carries a risk of bleeding that is ongoing throughout treatment. The CYP2C9 genotype carries a risk for major hemorrhage, with the highest risk being in the first three to six months after initiation of therapy.

The variant alleles of CYP2C9 and VKORC1 can explain 10%–45% of the dosage requirement variations for warfarin (Johnson & Cavallari, 2015). For example, the presence of the CYP2C9\*2 allele may lead to a 1 mg per day reduction. However, the presence of the VKORC1-1639AA allele may result in a 2–3 mg per day reduction, whereas the VKORC1-1639GG allele may cause a 1 mg per day increase.

### Clinical Guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that genotype information, when available, be used in determining warfarin dosage, noting that data support the predictive value of genetic information in warfarin dosing (Johnson & Cavallari, 2015). In addition, the CPIC recommends that algorithms detailed by Gage et al. (2008) and Klein et al. (2009) be used for dosage determination instead of the U.S. Food and Drug Administration (FDA) drug label data. Both algorithms use demographic data (e.g., age, height, weight, gender, race), clinical history, and genotype to recommend initial dosages for warfarin (Gage et al., 2008; Klein et al., 2009; PharmGKB,

2014). Gage et al. (2008) developed a website that allows healthcare providers to easily access the algorithms ([www.warfarindosing.org](http://www.warfarindosing.org)).

The FDA advises that when pharmacogenetic testing is used, it must be used cautiously and in collaboration with INR (Institute of Medicine, 2010). The clinical studies reported by Johnson and Cavallari (2015) used INR as the standard test to determine patients' therapeutic status of warfarin, regardless of the use of the genotype in setting initial dosage requirements. Zineh, Pacanowski, and Woodcock (2013) noted that the extensive use of INR in these studies may have actually contributed to the difficulty in determining the effectiveness of the use of genotype results. Measurement of INR is, and likely will continue to be, the standard of care in determining and monitoring the therapeutic range of warfarin.

The package insert for Coumadin®, a brand name for warfarin sodium, suggests that the initial and maintenance dosages of warfarin be adjusted depending on the presence of gene variations of CYP2C9 or VKORC1, if known (Bristol-Myers Squibb Pharma Company, 2011). In a statement that announced the addition of genetic information to warfarin packaging, the FDA (2007) noted that it supports the use of personalized medicine and pharmacogenomics to help identify optimal dosages for individual patients. However, the FDA (2007) also explained that more studies are needed to determine the precise drug dosages for patients with genetic variations. Although the FDA has approved some test kits for warfarin pharmacogenetic testing, the drug label does not overtly

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