

WARFARIN GENETICS AND DOSING: THE NEW PHARMACOGENOMIC FRONTIER

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A wide variation in dose-response and frequent bleeding complications characterize the initiation of warfarin therapy. Genetic determinants of warfarin dose-response have recently been identified. Therefore, a comprehensive pharmacogenetics approach to warfarin therapy has the potential to improve the safety and effectiveness of warfarin initiation. Maintenance warfarin dosing can be estimated from demographic, clinical, and pharmacogenetic factors.

Some patients have an extremely low warfarin dose requirement of 1.5 mg or less in the absence of liver dysfunction, drug interaction, or concomitant disease. They usually possess CYP2C9 variant alleles associated with impaired hydroxylation of S-warfarin. If their warfarin pharmacogenetic profile is not known when warfarin is initiated, these individuals have a potentially high risk of bleeding complications. Screening for CYP2C9 variants, with rapid turnaround of the results, may allow clinicians to develop individualized dosing protocols to reduce the risk of excessive anticoagulation.

Some patients have an extremely high warfarin dose requirement that exceeds 10 mg daily. Recently, vitamin K receptor gene haplotypes have been discovered that can help stratify patients into low, intermediate, or high dose warfarin groups. Variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) explain about 25% of the variance in warfarin dosage. Genetic profiles from CYP2C9 and VKORC1 can be combined to improve categorization of individual warfarin dose requirements.

The American Enterprise Institute and the Brookings Institute (www.aei-brookings.org) collaborated to study the potential impact of rapid turnaround genetic testing for warfarin. Their report was published in November 2006 and is entitled: "Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin." Their conclusions are illuminating: "We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate

the reduced health care spending from integrating genetic testing into warfarin therapy to be \$1.1 billion annually."

On January 18, 2007, Partners Healthcare System launched the CROWN Trial: **CR**eating an **Optimal Warfarin Nomogram**. This is a 500-patient cohort to study rapid turnaround genetic testing in patients who require initiation of warfarin. The goal is to achieve and maintain the target INR between 2.0 and 3.0 at least 70% of the time. The nomogram will combine genetic and clinical information to optimize warfarin dosing. If successful, CROWN will herald a new era in which pharmacogenomics transforms and personalizes medicine for a common problem, warfarin dosing, that has frustrated clinicians for more than 50 years.

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