## Personalized Medicine Corner

# Is there a benefit for pharmacogenomic testing with warfarin?

Warfarin is an anticoagulant associated with high bleeding risk and variable dose requirements that are influenced by clinical (e.g., age, weight, and concomitant medications) and genetic (e.g., *CYP2C9* and *VKORC1* genotype) factors. The *CYP2C9* gene codes for the major warfarin metabolizing enzyme, and *VKORC1* codes for vitamin K reductase, the target protein of warfarin. Dosing algorithms that use genotype and clinical variables are available to assist with dosing (i.e., WarfarinDosing.org). If genotype is not known, the algorithm recommends a dose based on clinical factors, a strategy that has been shown to be more accurate than the traditional approach of starting at 5 mg/day.[1]

Results of clinical trials examining the use of genotype to guide warfarin dosing have varied.[2] In a European trial, use of pharmacogenetic information to dose warfarin was more accurate than a traditional dosing approach.[3] A trial in the U.S., published at the same time, showed that use of a dosing algorithm with genotype provided no benefit over an algorithm that used only clinical factors.[4] However, the U.S. trial has been criticized for not using loading doses or including genotypes important for African Americans who made up nearly 30% of the study population. Although the Center for Medicare and Medicaid Services (CMS) does not pay for warfarin pharmacogenetic testing outside of a clinical trial, some institutions still offer testing to assist with warfarin dosing based on the significant evidence that genotype influences dose requirements.

A recent post-hoc analysis of the ENGAGE AF-TIMI 48 trial published in *Lancet* provided additional evidence to support pharmacogenetic testing for warfarin.[5] ENGAGE AF–TIMI 48 was a prospective, randomized study that compared the oral factor Xa inhibitor edoxaban to warfarin titrated to an International Normalized Ratio (INR) of 2-3 in over 20,000 individuals with atrial fibrillation. The study found that edoxaban was noninferor to warfarin for preventing stroke and systemic embolism with significantly fewer major bleeding events. In a post-hoc analysis, investigators compared clinical events according to *CYP2C9* and *VKORC1* genotypes: among patients assigned to warfarin, genotype combinations associated with increased sensitivity to warfarin conferred a higher risk for over-anticoagulation and overt bleeding events in the first 90 days of therapy. Edoxaban was associated with lower bleeding risk compared to warfarin in those with a highly sensitive genotype, but not in those with a normal response genotype.

Investigators noted that these study results demonstrated "clear and significant associations" between *CYP2C9* and *VKORC1* genotypes and warfarin bleeding outcomes and supported the role of genetic data in complementing traditional clinical predictors of adverse effects with warfarin.[5] An accompanying editorial called for CMS to reconsider their position on reimbursement for pharmacogenetic testing for warfarin so that individuals with warfarin sensitive *CYP2C9* and *VKORC1* can be offered alternative anticoagulant medications.[6] Additional trials of pharmacogenetic dosing of warfarin are on-going.[2]

References:
1. Klein TE, et al. *N Engl J Med* 2009;360:753-64.
2. Cavallari LH, et al. *Clin Pharmacol Ther* 2014;96:22-4.
3. Pirmohamed M, et al. *N Engl J Med* 2013;369:2294-303.
4. Kimmel SE, et al. *N Engl J Med* 2013;369:2283-93.
5. Mega JL, et al. *Lancet* 2015;385:2280-7.
6. Wu AH. *Lancet* 2015;385:2231-2.

*Co-Editors:* Larisa Cavallari, PharmD; Kristin Weitzel, PharmD; *Associate Editor:* Siegfried O. Schmidt, MD, PhD; *Assistant Editor:* Miguel Ramos, PharmD

The Personalized Medicine Corner appears quarterly and is provided by the UF Health Personalized Medicine Program. To find out more or submit a question, email PMP-HELP@ctsi.ufl.edu.

**PharmaNote®**

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida