Clinical utility of warfarin pharmacogenomics

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TO THE EDITOR: We previously addressed whether *VKORC1* and *CYP2C9* pharmacogenomic testing should be considered when prescribing warfarin.[1] Our recommendation, based on available evidence at that time, was that physicians should consider pharmacogenomic testing for any patient who is started on warfarin therapy.

Since the publication of this recommendation, two major trials, COAG (Clarification of Optimal Anticoagulation Through Genetics)[2] and EU-PACT (European Pharmacogenetics of Anticoagulant Therapy-Warfarin),[3] were published along with commentaries debating the clinical utility of warfarin pharmacogenomics.[4–15] Based on these publications, we would like to update our recommendations for pharmacogenomic testing for warfarin therapy.

COAG compared the efficacy of a clinical algorithm or a clinical algorithm plus *VKORC1* and *CYP2C9* genotyping to guide warfarin dosage. At the end of 4 weeks, the mean percentage of time within the therapeutic international normalized ratio (INR) range was 45.4% for those in the clinical algorithm arm and 45.2% for those in the genotyping arm (95% confidence interval [CI] –3.4 to 3.1, $P = .91$). For both treatment groups, clinical data that included body surface area, age, target INR, concomitantly prescribed drugs, and smoking status were used to predict warfarin dose, with the genotyping arm including *VKORC1* and *CYP2C9*. Although *VKORC1* and *CYP2C9* genotyping offered no additional benefit, caution should be used when extrapolating this conclusion to clinical settings in which warfarin therapy is initiated using a standardized starting dose (eg, 5 mg daily) instead of a clinical dosing algorithm.

Of interest, in the COAG trial, among black patients, the mean percentage of time in the therapeutic INR range was significantly less for those in the genotype-guided arm than for those in the clinically guided arm—ie, 35.2% vs 43.5% (95% CI –15.0 to –2.0, $P = .01$). The percentage of time with therapeutic INR has been identified as a surrogate marker for poor outcomes such as death, stroke, or major hemorrhage, with those with a lower percentage of time in therapeutic INR being at greater risk of an adverse event.[16] Wan et al[17] demonstrated that a 6.9% improvement of time in therapeutic INR decreased the risk of major hemorrhage by one event per 100 patient-years.[17] Therefore, black patients in the COAG genotyping arm may have been at greater risk for an adverse event because of a lower observed percentage of time within the therapeutic INR range.

In the COAG trial, genotyping was done for only one *VKORC1* variant and for two *CYP2C9* alleles (*CYP2C9*2*, and *CYP2C9*3*). Other genetic variants are of clinical importance for warfarin dosing in black patients, and the lack of genotyping for these additional variants may explain why black patients in the genotyping arm performed worse.[5,7,11] In particular, *CYP2C9*8* may be an important predictor of warfarin dose in black patients.[18]

EU-PACT compared the efficacy of standardized warfarin dosing and that of a clinical algorithm.[3] Patients in the standardized dosing arm were prescribed warfarin 10 mg on the first day of treatment (5 mg for those over age 75), and 5 mg on days 2 and 3, with subsequent dosing adjustments based on INR. Patients in the genotyping arm were prescribed warfarin based on an algorithm that incorporated clinical data that included body surface area, age, and concomitantly prescribed drugs, as well as *VKORC1* and *CYP2C9* genotypes. At the end of 12 weeks, the mean percentage of time in the therapeutic INR range was 60.3% for those in the standardized-dosing arm and 67.4% for those in the genotyping arm (95% CI 3.3 to 10.6, $P < .001$).[2] The approximate 7% improvement in percentage of time in the therapeutic INR range may predict a lower risk of hemorrhage for those in the genotyping arm.[17] Although patients in the genotyping arm had a higher

percentage of time in the therapeutic INR range, it is unclear whether genotyping alone is superior to standardized dosing because the dosing algorithm used both clinical data and genotype data.

There are substantial differences between the COAG and EU-PACT trials, including dosing schemes, racial diversity, and trial length, and these differences could have contributed to the conflicting results. Based on these two trials, a possible conclusion is that genotype-guided warfarin dosing may be superior to standardized dosing, but may be no better than utilizing a clinical algorithm in white patients. For black patients, additional studies are needed to determine which genetic variants are of importance for guiding warfarin dosing.

We would like to update the recommendations we made in our previously published article,[1] to state that genotyping for *CYP2C9* and *VKORC1* may be of clinical utility in white patients depending on whether standardized dosing or a clinical algorithm is used to initiate warfarin therapy. Routine genotyping in black patients is not recommended until further studies clarify which genetic variants are of importance for guiding warfarin dosing.

The ongoing Genetics Informatics Trial of Warfarin to Prevent Venous Thrombosis may bring much needed clarity to the clinical utility of warfarin pharmacogenomics. We hope to publish a more detailed update of our 2013 article after completion of that trial.

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