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Race influences warfarin dose, study says

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A new report demonstrates that clinical and genetic factors affecting dose requirements for warfarin vary by race. The study, published online today in *Blood*, the Journal of the American Society of Hematology (ASH), proposes race-specific equations to help clinicians better calculate warfarin dosage.

Warfarin is the most widely used blood thinning medication, or anticoagulant, prescribed to prevent stroke and to treat blood clots. Determining the optimal warfarin dose to prevent clots while avoiding dangerous bleeding is difficult. To ensure that a safe balance is achieved, patients taking warfarin must regularly visit the doctor for blood tests.

Investigators have identified several factors that affect how the body breaks down warfarin and that consequently influence dose requirements. These include clinical factors such as height and weight and the presence of genes that help the body break down warfarin (*CYP2C9*) and help to activate clotting (*VKORC1*).

While researchers agree that these clinical and genetic factors affect individual patients' dose requirements, whether this translates to achieving and maintaining a safe level of anticoagulation was explored in two recent clinical trials with conflicting results.

In 2013, the EU-PACT trial reported that calculating a patient's warfarin dose based on the presence of genetic factors (known as genotype-guided dosing) improved anticoagulation control. Meanwhile, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial

reported that a similar genotype-guided dosing strategy did not appear to make a difference among patients enrolled. Of note, the COAG trial included more African Americans than EU-PACT (27% of the study population vs. 0.9%), and the African Americans enrolled actually fared worse after receiving genotype-guided therapy. According to a research group led by Nita Limdi, PhD, PharmD, MSPH, of the University of Alabama at Birmingham, the studies' disparate findings may be attributed to differences in racial diversity among participants.

"As the outcomes of disease can vary by race, so can response to medications," said Dr. Limdi. "Therefore, warfarin dosing equations that combine race groups for analysis (race-adjusted analysis) assume that the effect of variables - such as age and genetics - are the same across race groups, which may compromise dose prediction among patients of both races."

In order to better understand how genetics and clinical factors influence warfarin dose across race groups, investigators analyzed 1,357 patients (595 African American; 762 European American) treated with warfarin, calculating and comparing their recommended dose according to both race-adjusted dosing models (e.g., COAG) and race-specific dosing models. As 43 percent of the study population was African American, the research team was able to conduct a robust assessment of the impact of clinical and genetic factors on warfarin dose by race.

After calculating and comparing recommended warfarin dose for study participants according to race-combined dosing models and race-specific dosing models, researchers made several significant observations. While genetic factors accounted for a larger proportion of the dose variability for European American patients, clinical factors accounted for a larger dose variability in African Americans. They noted that gene variants may have a different effect on dose across race groups. For example, European Americans with a variant of *CYP2C9* (*CYP2C9*2*) required

less of the drug according to race-specific dosing models, yet African Americans did not. While all participants, regardless of race, who carried *VKORC1* required lower doses, according to race-specific dosing models, the proportional dose reduction was greater among European Americans.

Researchers conclude that the influence of genetic and clinical factors on warfarin dose differs by race, and therefore recommend that race-specific equations, rather than race-adjusted equations, be used to guide warfarin dosing.

"Our findings highlight the need for adequate racial representation in warfarin dosing studies to improve our understanding of how the factors that influence warfarin dose differ according to race," said Dr. Limdi. "This is the first step to developing race-specific algorithms to personalize therapy."

Provided by American Society of Hematology