New study finds no benefit to selecting dose of blood thinner based on patients' genetic makeup

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A new study led by researchers at the Perelman School of Medicine at the University of Pennsylvania has determined that a gene-based method for selecting patients' doses of the popular heart medication warfarin is no better than standardized dosing methods. The study was presented today at the 2013 Scientific Sessions of the American Heart Association and published simultaneously in the *New England Journal of Medicine*.

"There has been much interest in the medical community about the utility of pharmacogenetics – using information about a person's genetic makeup to choose the drugs and drug doses that are most likely to work well for that particular person – to help better personalize treatments for patients and improve drug safety and efficacy," said lead study author Stephen Kimmel, MD, MSCE, professor of Medicine and Epidemiology at Penn Medicine. "Warfarin therapy has served as a model for the promise of a gene-based approach to patient care, but we needed a large, prospective clinical trial to determine if a patient's genetic information provides the added benefit above and beyond what can be obtained simply with clinical information."

Warfarin is a blood thinner used to prevent clots and is generally considered to be a very effective medication, but dosing must be properly adjusted for each patient, who are closely monitored for complications. Approximately 2 million Americans, primarily older patients, take warfarin to keep blood from excessive clotting, or

coagulation. Currently, doctors face major challenges in determining the right dose of warfarin for each patient because individuals vary widely in how quickly their bodies' break down and respond to the drug. Taking too much warfarin could result in bleeding problems and taking too little warfarin will not stop clots from forming.

Previous research has shown that two genes, CYP2C9 and VKORC1, which vary among different individuals, can influence warfarin's effectiveness. In 2007 and 2010, the FDA worked with the makers of warfarin drug products to modify the product label to indicate that a patient's genetic makeup may affect how he or she responds to the drug and that genetic information might be useful in determining the optimal starting dose.

To find out whether these genes could help clinicians prescribe an optimal dose, the Clarification of Optimal Anticoagulation through Genetics (COAG) trial – consisting of 18 clinical sites across the country and funded by the National Heart, Lung and Blood Institute (NHLBI) – tested two approaches for determining the best initial dose of warfarin in patients who were expected to need therapy for at least one month or longer – by clinical information alone or by clinical information plus specific genetic information. The four-year study included 1,015 patients randomly assigned to one of two groups during the first five days of initiating warfarin therapy.

For the patients in the clinical-based dosing group, the initial warfarin dose was determined using step-by-step procedures based only on information about clinical factors, such as age, sex, weight, ethnicity, and the use of other medications. In the gene-based dosing group, the initial dose was determined using this same clinical information as well as information about the patient's genetic makeup, including analyzing the participants' DNA for the CYP2C9 and VKORC1 genes. Patients and their providers were blinded to the dose of warfarin for the first

month of therapy.

The researchers found that there was no difference among the two groups in mean percentage of time in therapeutic range (PTTR) for the medication (45.2 percent in the pharmacogenetic-dosing group versus 45.4 percent in the clinical-guided dosing group) at four-weeks. There was, however, a statistically significant difference by race. Among African Americans, the mean PTTR for the pharmacogenetic-guided dosing group was less than that for the clinical-guided dosing group – 35.2 percent versus 43.5 percent, respectively. Pharmacogenetic-based dosing also led to more over-anticoagulation and a longer time to first therapeutic levels of the warfarin among African Americans.

The authors note that despite the positive results from other smaller studies analyzing the benefits of gene-based prescribing therapy, the results of this trial do not support the hypothesis that initiating warfarin therapy at a pharmacogenetic-predicted maintenance dose improves anticoagulation control over clinical methods. They point out that previous studies were primarily conducted at single clinical sites, were not blinded, and involved a limited number participants. They conclude that the COAG trial emphasizes the importance of performing large randomized trials for additional pharmacogenetics approaches, particularly for complex medicine regimens such as warfarin.

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