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# Conclusive link between genetics and clinical response to warfarin uncovered

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In a study published in *The Lancet* on March 10, researchers from Brigham and Women's Hospital (BWH) report that patients with a genetic sensitivity to warfarin - the most widely used anticoagulant for preventing blood clots - have higher rates of bleeding during the first several months of treatment and benefited from treatment with a different anticoagulant drug. The analyses from the TIMI Study Group, suggest that using genetics to identify patients who are most at risk of bleeding, and tailoring treatment accordingly, could offer important safety benefits, particularly in the first 90 days of treatment.

"We were able to look at patients from around the world who were being treated with warfarin and found that certain genetic variants make a difference for an individual's risk for bleeding," said Jessica L. Mega, MD, MPH, a cardiologist at BWH, senior investigator in the TIMI Study Group and lead author of the paper. "For these patients who are sensitive or highly sensitive responders based on genetics, we observed a higher risk of bleeding in the first several months with warfarin, and consequently, a big reduction in bleeding when treated with the drug edoxaban instead of warfarin."

Warfarin has been in clinical use for 60 years and genetics has been thought to influence an individual's sensitivity to the drug. The FDA label for warfarin notes that genetic variants in two genes - CYP2C9 and VKORC1 - can assist in determining the right warfarin dosage for an individual. But a conclusive link between variation in these two genes and bleeding has been debated. By leveraging data from their ENGAGE

AF-TIMI 48 trial - an international, randomized, double-blind trial in which patients with atrial fibrillation received either a higher dose of edoxaban, a lower dose of edoxaban or warfarin to prevent blood clots from forming in the heart and leading to stroke - the TIMI investigators were able to observe important connections between genetic differences and patient outcomes. The trial represents the largest study of this kind to date and included nearly three years of follow-up with participants.

In ENGAGE-TIMI 48, patients were randomly assigned treatment and followed over time. The research team divided 14,000 study participants into three categories based on genetic makeup: normal responders, sensitive responders or highly sensitive responders. During the first 90 days, sensitive and highly sensitive responders who received warfarin experienced significantly higher rates of bleeding compared to normal responders. As a result, during this early time period, edoxaban was more effective than warfarin at reducing bleeding in sensitive and highly sensitive responders.

"These findings demonstrate the power of genetics in personalizing medicine and tailoring specific therapies for our patients," said Marc S. Sabatine, MD, MPH, a cardiologist at BWH, Chairman of the TIMI Study Group and senior author of the paper.

Warfarin remains the most common anticoagulant in part due to economics and availability, but several novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban and apixaban, have entered the market. Edoxaban, a Xa inhibitor, received FDA approval for stroke prevention in atrial fibrillation earlier this year based on the results of the ENGAGE AF-TIMI 48 trial.

Provided by Brigham and Women's Hospital