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WARFARIN DOSING ALGORITHM REFINEMENTS AFTER 7-9 DAYS OF THERAPY BASED ON PHARMACOGENETIC, PHARMACOKINETIC, CLINICAL, AND LABORATORY DATA

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Authors: *Benjamin D. Horne, Petra A. Lenzini, Mia Wadelius, Andrea L. Jorgensen, Stephen E. Kimmel, Niclas Eriksson, Jeffrey L. Anderson, Munir Pirmohamed, Nita A. Limdi, James K. Burmester, Daniel Kurnik, Charles M. Stein, Michael D. Caldwell, Charles S. Eby, Anders Rane, John D. Lindh, Jae-Gook Shin, Ho-Sook Kim, Pantep Angchaisuksiri, Jinbo Chen, John F. Carlquist, Gloria R. Grice, Kathryn E. Kronquist, Brian F. Gage, Intermountain Medical Center, Murray, UT, University of Utah, Salt Lake City, UT*

Background: Pharmacogenetic (PGx) dosing algorithms have potential to improve the safety of warfarin initiation and have been developed to guide the initial warfarin dose(s). However, INR response to the initial doses reflects warfarin sensitivity and researchers question the relevance of genotype once INR data are available. To test the hypothesis that genotype is relevant after a week of warfarin therapy, we developed PGx and clinical algorithms to predict the stable warfarin dose using genotype, INR response on days 7-9 of therapy, and clinical factors.

Methods: We collected clinical, laboratory, and genetic data in an international sample (n=913) across 3 continents. We considered genotype, INR response, and clinical variables (current medications, warfarin indication, height, weight, and demographic factors). To accommodate collinear daily warfarin doses, we averaged prior doses weighted by their expected effect on warfarin concentrations at the time the INR was drawn. We used stepwise regression to develop dose refinement algorithms and retained variables that were significant independent predictors of stable warfarin dose (i.e., $p<0.05$) or that were biologically compelling.

Results: In both the PGx and clinical refinement algorithms, prior doses, body surface area, and target INR predicted higher therapeutic warfarin dose, while INR, age, and amiodarone predicted lower dose. The PGx algorithm added CYP2C9 *2 and *3 genotypes and VKORC1-1639 G->A genotype as predictors of lower therapuetic dose. The PGx algorithm explained significantly ($p<0.0001$) more dose variation ($R2 = 68\%$) than the clinical algorithm ($R2 = 54\%$). The PGx algorithm also had a substantially lower ($p<0.0001$) median absolute error (5.2 mg/week) than the clinical algorithm (6.1 mg/week).

Conclusions: After 7-9 days of therapy, a warfarin dose-refinement algorithm incorporating PGx data provided substantially better prediction of therapeutic warfarin dose and can explain two-thirds of the variability in stable warfarin dose. Because intermittent INR monitoring is the standard practice in the outpatient setting, such an algorithm will be of substantial value among outpatients receiving warfarin therapy.