Development of a Universal Pharmacogenetics-guided Warfarin Dosing Nomogram

Jiexin Deng¹, Meghan Arwood², Julio Duarte², Larisa Cavallari², Stephan Schmidt¹

¹Center for Pharmacometrics & Systems Pharmacology, Univ. of Florida, Orlando, FL; ²Pharmacotherapy and Translational Research and Center for Pharmacogenomics, Univ. of Florida, Gainesville, FL

Objectives: Although warfarin is a widely prescribed drug, suboptimal dosing may cause serious complications including bleeding and thrombosis. Genotype-guided algorithms, such as warfarindosing.org, have been primarily developed based on data from Caucasians on stable warfarin dosing. The objective of our study was to develop a dosing nomogram that can facilitate optimal dosing in a diverse population.

Methods: Data from patients of diverse ethnicities (57% African Americans and 17% Hispanics) initiating warfarin with genotype-guided dosing (warfarindosing.org) were used in this study. Data management and exploratory analysis were performed in R (version 3.2.1). The Rosendaal method was used to calculate time in therapeutic range, assuming linear change between two consecutive INR measurements. A mechanism-based model characterizing warfarin dose/response was developed based on Hamberg et al. in NONMEM® (version 7.3). Initiation nomogram consisting of loading and maintenance dosing were developed based on simulations in virtual individuals of different ages, genotypes (VKORC1 and CYP2C9), and ethnicities.

Results: Exploratory analysis indicates that our patients spent less time in therapeutic range compared to Europeans in the EU-PACT trial (55% vs. 65%) at 70-90 days of therapy, which is consistent with literature reports of suboptimal performance of genotype-guided algorithms in African Americans. To overcome this shortcoming, we developed a dynamic dosing nomogram that could enable patients to reach therapeutic INR within 1 week and remain stable across genotypes and ethnicities (Fig. 1). Furthermore, our maintenance doses were consistent with dose recommendations across different combinations of VKORC1 and CYP2C9 as shown on the FDA approved label for warfarin.

Conclusions: We developed the first pharmacogenetic-guided warfarin initiation nomogram that accounts for its dynamic dose-response relationship to facilitate optimal dosing in a diverse population.

References:
2. Hamberg et al., CPT 87(6): 727-734, 2010