Leveraging Prior Quantitative Knowledge Demonstrates the Importance of Genotype-based Dosing of Warfarin

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Introduction: Warfarin is an oral anticoagulant most frequently used for the treatment and/or prevention of thromboembolic events. The drug has a narrow therapeutic index and its optimal anticoagulation therapy requires achieving and maintaining a target International Normalized Ratio (INR). A significant number of factors play a role in achieving and maintaining the INR within its target range and a high between patient variability in therapeutic dose requirement has been observed.

Objective: To leverage prior information on PK, PD, and genetic variations, thereby optimizing warfarin dosing algorithms to be studied in future trials.

Methods: We performed a thorough literature search on information about warfarin therapy pertaining to metabolic variation due to factors such as weight, age and CYP2C9 genotype status; relationship between concentration-INR; and influence of VKORC1 genotype status on the IC50. The mechanistic concentration-INR relationship reported in the literature, together with the effects of known prognostic factors was employed to analyze data from a new study of 71 patients treated with warfarin up to 90 days. The model and the parameter estimates were utilized to explore competing dosing regimens. These regimens were compared using the proportion of patients below, within and above a target INR of 2-3.

Results: The mechanistic model described the time-course of INRs from the 71 patients well. We faced several challenges during this analysis, which ranged from conflicting literature reports, lack of PK data, variations on the PKPD model to wide disagreements on the IC50 estimates. The simulations suggest that CYP2C9 and VKORC1 genotype status plays an important role in warfarin dosing. In addition, the choice of the warfarin titration strategy influences the time and the proportion of patients reaching target INR.

Conclusion: In silico modeling of prior quantitative information indicates that genotype based dosing and an optimized titration scheme play an important role in optimizing warfarin therapy.