

Title: Evaluation of Warfarin Therapy Management Protocols via PK/PD Simulation

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Objectives: Each year, an estimated 2 million people start taking warfarin [1], an anticoagulant commonly prescribed for long term prevention of thromboembolic events. Appropriate dosing of warfarin can be challenging. Approximately 30% to 40% of patients may be receiving suboptimal doses of the drug, as measured by prothrombin times and INR values [1]. Due to such challenges, there remains significant interest in dosing strategies for warfarin. Published algorithms for initiation and/or maintenance of warfarin therapy include paper-based dosing algorithms [2, 3]. Many clinicians follow such algorithms in general, but individualize dose adjustments and INR monitoring based on specific patient data/histories. Furthermore, the incorporation of genetic information to guide dosing decisions is being considered and evaluated. Computer simulation of this personalized medicine approach is a powerful tool to explore dosing and treatment scenarios conditional on what is known about the pharmacokinetics (PK) and the pharmacodynamics (PD) of a drug, in addition to population demographics and other relevant covariates, such as genetic polymorphisms. Our objectives in this work are: (1) to develop a PK/PD, model-based simulation approach for prediction of variable clinical outcomes related to genetic and non-genetic variation; and (2) to utilize this approach to compare simulated population study results of various published and unpublished warfarin dosing strategies. The simulation approach must be flexible enough to capture the complexities, both stated and hidden, of various warfarin administration protocols. This work is part of our larger effort to model the long term clinical and economic implications of various genetic and non-genetic -based warfarin dosing strategies.

Methods: We simulated the disposition (concentration time course) and clinical effect (INR time course) of oral warfarin administration (see Figure) by implementing a recently published population PK/PD model [4, and personal communication]. The NONMEM software system, Version VI, was used [5]. Effects of genetic variation in the *CYP2C9* (PK) and *VKORC1* (PD) genes are included in the model. Age is also included, since it was found to be a relevant demographic covariate for warfarin disposition [4]. We developed a flexible protocol simulation routine in R [6] and used it to implement various adaptive dosing strategies, from warfarin initiation through a 60-day time horizon. Simulation complexities include tracking of individual-specific events, such as appointment scheduling and the timing of the switch from initiation to the maintenance stage of an algorithm. Population demographic variability in age, baseline INR, and *CYP2C9* and *VKORC1* genotype were sampled from distributions based on reported patient demographics in [4]. Each protocol was preliminarily tested on the same set of 500 simulated test subjects; 500 subjects were found to be a large enough sample that changes in random seed had very little effect on overall results. Results obtained by repeatedly sub-sampling 250 subjects out of 500 were substantially similar to the results conditional on the entire sample size.

Results: The simulation strategy outlined above is feasible (running times were less than 80 minutes on a 3GHz PC) to compare and evaluate various warfarin dosing protocols. Based on published information, we conclude that the simulated PK and PD results are plausible. As this work progresses, we will report, for each simulated protocol, percent of time in range ($2 < \text{INR} < 3$) and above ($\text{INR} > 3$) and below ($\text{INR} < 2$) range during the first and second month of therapy. This will be done for all patients, as well as for patients stratified as *CYP2C9* variants; *CYP2C9* wild type and *VKORC1* BB; and *CYP2C9* wild type and *VKORC1* AA and AB.

Conclusions: We developed a computational platform, integrating R and NONMEM, to simulate dosing algorithm administration for warfarin, using a state of the art PK/PD model and plausible patient demographics. Future work will include comparison of population INR results from application of published and unpublished protocols and integration with pharmacoeconomic information to determine the cost efficacy of genetic and non-genetic dosing algorithms.

References:

[1] Landers SJ. Focus turns to how genetics impacts warfarin therapy. AMNews. Sept. 10, 2007

- [2] Kovacs MJ, Rodger M, Anderson DR, et al (2003). Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. *Ann. Intern. Med.* 138 (9): 714-9.
- [3]. Wilson SE, Costantini K., Crowther MA. (2007) Paper-based dosing algorithms for maintenance of warfarin anticoagulation. *Journal of Thrombosis and Thrombolysis* 23:3, 195-198.
- [4] Hamberg A-K, Dahl M-L, Barban M, Scordo M G, Wadelius M, Pengo V, Padrini R and Jonsson EN (2007) A PK-PD Model for Predicting the Impact of Age, CYP2C9, and VKORC1 Genotype on Individualization of Warfarin Therapy *Clinical Pharmacology & Therapeutics* (2007) 81, 529–538.
- [5] NONMEM Users Guides, (1989-98). Beal, S.L. and Sheiner L.B. (Eds.), Icon Development Solutions, Ellicott City, Maryland, USA.
- [6] R Development Core Team (2006). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>.

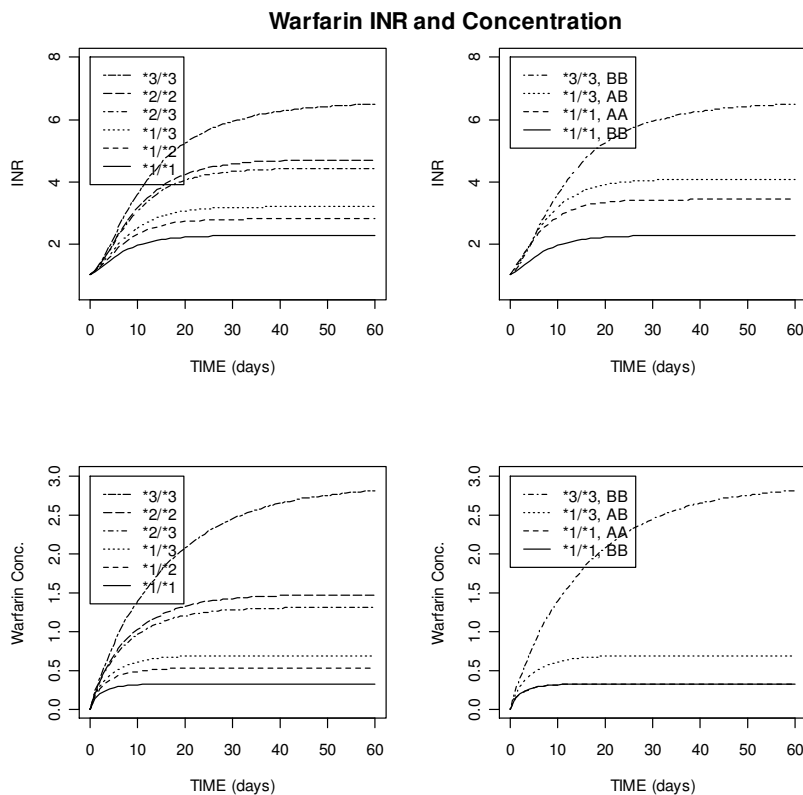


Figure Warfarin INR (top row, as in [4]) and concentration (bottom row) for 50 year old subjects receiving 4 mg per day warfarin. Results are displayed by *CYP2C9* polymorphism (left graphs) and for specified *CYP2C9* and *VKORC1* polymorphisms (right graphs). Notice the lag in time between concentration and effect (INR).