**Introduction**

Warfarin is the oral anticoagulant most frequently used for long-term 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 requirements has been observed.

**Objective**

To leverage prior information on PK, PD and genetic variation, thereby optimizing warfarin dosing algorithm 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 relationship report in the literature, together with the effects of known prognostics 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. Those regimens were compared using the proportion of patients below, within and above a target INR of 2-3.

**Analysis strategy :**

- **Prior Knowledge:** Warfarin mechanism and update our dosing algorithm as new data accrue.
- **Mechanical Model:** Warfarin mechanistic model
- **Simulation strategy:** Simulation conditions
- **Results:** Warfarin mechanism being used in a current study
- **Titration schemes:** CR : titration scheme being used in a current study
- **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.

**Simulation conditions:**

- 10,000 patients per arm
- Study period: 90 days
- Dose is given once / day and adjusted twice per week
- Starting dose (previous table) is given for the first 4 days
- From day 5, dose is adjusted based on the measured INR using a titration scheme

**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 and variations on PK/PD model to wide disagreements on the IC50 estimates. The simulations suggest that CYP2C9 and VKORC1 genotype status play an important role in warfarin dosing.
- In addition, the choice of the warfarin titration strategy influences the time and proportion of patients reaching and maintaining 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.

**References**

- Hamberg et al ; CPT (2007)
- Chan et al ; CPT (1994)
- Robert S. Kidd and Arthur F. Harralson (Shenandoah University)