External Evaluation of a Bayesian Warfarin Dose Optimization Based on a Kinetic-Pharmacodynamic Model

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Warfarin is a representative anticoagulant with large interindividual variability. The published kinetic-pharmacodynamic (K-PD) model allows the prediction of warfarin dose requirement in Swedish patients; however, its applicability in Japanese patients is not known. We evaluated the model’s predictive performance in Japanese patients with various backgrounds and relationships using Bayesian parameter estimation and sampling times. A single-center retrospective observational study was conducted at Tokyo Women’s Medical University, Medical Center East. The study population consisted of adult patients aged >20 years who commenced warfarin with a prothrombin time-international normalized ratio (PT-INR) from June 2015 to June 2019. The published K-PD model modified by Wright and Duffuss was assessed using prediction-corrected visual predictive checks, focusing on clinical characteristics, including age, renal function, and individual prediction error. The external dataset included 232 patients who received an initial warfarin daily dose of 3.2 ± 1.28 mg with 2278 PT-INR points (median [range] follow-up period of 23 d [7–28]). Prediction-corrected visual predictive checks carried a propensity for underprediction. Additionally, age >60 years, body mass index ≤25 kg/m², and estimated glomerular filtration rate ≤60 ml/min/1.73 m² had a pronounced tendency to underpredict PT-INR. However, Bayesian prediction using four prior observations reduced underprediction. To improve the prediction performance of these special populations, further studies are required to construct a model to predict warfarin dose requirements in Japanese patients.

Key words warfarin; prothrombin time-international normalized ratio; Bayesian dosing; renal function

INTRODUCTION

Warfarin is a traditional oral anticoagulant that inhibits the inactivation of clotting factor synthesis by vitamin K epoxide reductase in patients with cardiogenic embolism or heart valve replacement. In the clinical setting, warfarin has an extremely large interindividual variability; therefore, clinicians should frequently monitor the international normalized ratio of prothrombin time (PT-INR) as an index of anticoagulation conditions to adjust warfarin dose requirements. For instance, the target PT-INR range is 2.0 to 3.0 in patients with stroke.

The variability in warfarin dose requirement results from age, body size, and genetic variants of CYP2C9 and vitamin K oxide reductase complex (VKORC1). To optimize warfarin dose requirements, pharmacometric models incorporating these variables have been tested in Swedish patients receiving warfarin therapy. Bayesian dose optimization using the kinetic-pharmacodynamic (K-PD) model has a tendency to overpredict the maintenance dose at doses of 7 mg/d and higher. However, Japanese patients have a different profile in the genetic variants of CYP2C9 and VKORC1. Maintenance doses have been reported to be overestimated at doses above 6 mg/d using the K-PD model in Chinese individuals, who have a similar genetic background to the Japanese. The predictive performance of the warfarin K-PD model may vary depending on racial and ethnic differences. Additionally, these effects explain only 50% of the individual variability of warfarin. Recently, profound attention has been focused on the role of renal impairment and drug–drug interactions, such as amiodarone, in the risk of bleeding events associated with warfarin.

We reported the usefulness of warfarin dose optimization using the K-PD model in Japanese patients by clinical trial simulations, but to the best of our knowledge, there is no report in a real-world dataset that contains patient characteristics such as renal function and concurrent medications.

This study aimed to investigate whether Bayesian dose optimization using the K-PD model was useful for determining the initial warfarin dosage in Japanese patients with various backgrounds, such as those with renal impairment or those concurrently using amiodarone.

MATERIALS AND METHODS

Study Design and Patients This was a single-center retrospective observational study. The study site was at Tokyo Women’s Medical University, Medical Center East (450 beds, University Hospital, Tokyo, Japan). The study enrolled adult patients aged >20 years who commenced warfarin therapy with PT-INR measurements from June 2015 to June 2019. This study was approved by the institutional review board of Tokyo Women’s Medical University (5307) and Nihon University (19-007) in compliance with the Declaration of Helsinki.

Data Collection We surveyed the electrical medical chart to generate an external dataset as follows: demographic data...
(sex, age, height, body weight, fat-free mass, lean body weight, and body mass index), laboratory data (serum albumin, blood urea nitrogen, serum creatinine, and PT-INR), warfarin treatment (dose, dosing interval, and dosing period), and medications of interest (antiplatelet medications and amiodarone). Antiplatelet medications include low-dose aspirin, ticlopidine, clopidogrel, prasugrel, and cilostazol. Renal function was assessed using the prediction equation of estimated glomerular filtration rate (eGFR) as follows: eGFR = 194 × age⁻⁰.₂₈₇ × serum creatinine⁻¹.₉₉₄ × 0.₇₃₉ (if female).¹⁹ Longitudinal data were extracted from patients who had PT-INR measured at least five times during the first 28d of treatment. The follow-up period was from the introduction of warfarin therapy to the withdrawal of warfarin therapy or June 2019. Normally distributed data are expressed as mean ± standard deviation, and non-normally distributed data are expressed as median and range. Categorical data were expressed as numbers (%).

**K-PD Model of Warfarin**

In this study, we applied a published warfarin K-PD model outputting PT-INR from each dose in Swedish modified by Wright and Duffull.²⁰ The previous paper contains details of this model for S-warfarin, which has three to five times higher anticoagulation potency than R-warfarin. Basic S-warfarin pharmacokinetics describes the amount of the body; eGFR as follows:

\[ eGFR = \frac{1.23 \times BW (kg) \times 9.74 \times BMI (kg/m^2) + 0.0148 \times BW (kg) + 7.71 \times BMI (kg/m^2) \times 0.5178}{E_{max} \times DR} \]

where \( E_{max} \) is the maximum inhibition of coagulation set at 1, \( \gamma \) is a Hill coefficient (1.15), \( MTT_1 \) and \( MTT_2 \) are the mean transit time (28.6 and 118.3 h, respectively), \( INR_{pred} \) is the predicted PT-INR, \( INR_{BASE} \) is the dose rate for 50% inhibition of coagulation, \( EC_{50} \) is the S-warfarin concentration for 50% inhibition of coagulation (4.10 mg/L), \( EFF \) is an inhibitory effect, \( E_{max} \) is the maximum inhibition of coagulation set at 1, and \( \gamma \) is a Hill coefficient (1.15). The prediction formula of eGFR was as follows:

\[ eGFR = \text{max} \times \frac{(1 + (C1_a + C2_a))}{2} \]

\[ INR_{pred} = INR_{BASE} + INR_{max} \times (1 - (C1_b + C2_b)) \]

**Table 1. Patient Characteristics**

| Characteristics                  | N = 232 |
|----------------------------------|--------|
| **Demographical**                |        |
| Male, N (%)                      | 131 (56.5) |
| Age, years                       | 72 [26–96] |
| Age >60 years, N (%)             | 185 (79.7) |
| Height, cm                       | 160 [133–185] |
| Body weight, kg                  | 54.6 [33.0–103.0] |
| Lean body weight, kg             | 42.2 [24.6–72.3] |
| Body mass index, kg              | 44.9 [25.8–69.4] |
| BMI, kg/m²                       | 21.7 [14.0–36.0] |
| BMI ≤25 kg/m², N (%)             | 185 (79.7) |
| **Laboratory data**              |        |
| Serum albumin, g/dL              | 2.9 [1.4–4.7] |
| Blood urea nitrogen, mg/dL       | 18.6 [4.9–98.9] |
| Serum creatinine, mg/dL          | 0.94 [0.31–13.2] |
| eGFR², mL/min/1.73 m²            | 47.4 [2.6–199.0] |
| eGFR² ≤60 mL/min/1.73 m², N (%)  | 178 (76.7) |
| **Warfarin**                     |        |
| Initial warfarin daily dose, mg  | 3 [0.5–10] |
| **Medications of interest**      |        |
| Antiplatelet medications, N (%)  | 45 (19.4) |
| Low-dose aspirin, N (%)          | 34 (14.7) |
| Ticlopidine, N (%)               | 1 (0.4) |
| Clopidogrel, N (%)               | 7 (3.0) |
| Prasugrel, N (%)                 | 0 (0.0) |
| Cilostazol, N (%)                | 8 (3.4) |
| Amiodarone, N (%)                | 23 (9.9) |

Data represents median [range] or number (%). Abbreviations: N, number; BMI, body mass index; eGFR, estimated glomerular filtration rate. a) Fat-free mass (kg) was calculated using the following equations: 0.287 × BW (kg) + 12.1 × HT (m²) for males; 0.287 × BW (kg) + 9.74 × HT (m²) for females. Lean body weight (kg) was calculated using the following equations: 1.1 × BW (kg) − 0.0128 × BMI (kg/m²) × BW (kg) for males; 1.07 × BW (kg) − 0.0148 × BMI (kg/m²) × BW (kg) for females. where BW, BMI, and HT represent body weight, body mass index, and height, respectively. b) The prediction formula of eGFR was as follows: eGFR = 194 × age⁻⁰.₂₈₇ × serum creatinine⁻¹.₉₉₄ × 0.₇₃₉ (if female). Antiplatelet medications include low-dose aspirin, ticlopidine, clopidogrel, prasugrel, and cilostazol.
the baseline of PT-INR, and INR\textsubscript{max} is the theoretical maximum PT-INR set at 20. The inter-subject variability of CL, Vd, and EC\textsubscript{50} was 29.8, 23.2, and 33.2 CV\%, respectively. The intra-subject variability was 20 CV\%. We estimated individual K-PD parameters and simulated PT-INR using “MAXEV=0” and the First Order Conditional Estimates Interaction method in the SESTIMATION step of NONMEM software (version 7.4).

**External Evaluation of Kinetic-Pharmacodynamic Model** The external evaluation of the K-PD model performance was used visual and mathematical methods. We visually compared observed against predicted PT-INR by prediction-corrected visual predictive check (pc-VPC)\textsuperscript{21,22} with time, demographic data, and laboratory data as independent variables, or stratified based on the presence of concurrent medications, which was generated by simulating 500 replicates of the dataset. The pc-VPC was performed in NONMEM via Wings for NONMEM and the tidyvpc package in R (version 4.0.3).

Next, we assessed the relationship between individual prediction error (IPE) and the number of prior samples using Bayesian prediction to identify the number of prior observations on model performance. The IPE was calculated using the following IPE equation:

\[
\text{IPE}(\%) = \left( \frac{\text{IPRED} - \text{OBS}}{\text{OBS}} \right) \times 100 \tag{13}
\]

where IPE is the individual prediction error, IPRED is the individual predicted PT-INR, and OBS is the observed PT-INR. The percentage of absolute IPEs within 20% was assessed for each sampling time. The number of samples using Bayesian estimation was set from zero to five.

**RESULTS**

**Patient Backgrounds** This study included 232 patients who underwent warfarin therapy. The patient characteristics are summarized in Table 1. The study patients had a median age (range) of 72 (26–96) years. The median eGFR was 47.4 (2.6–199.0) mL/min/1.73 m\(^2\). There were 178 (76.7\%) patients who met the criteria for chronic kidney disease. Forty-five patients (19.4\%) received concurrent antiplatelet therapy.
Twenty-three patients (9.9%) received concurrent amiodarone therapy. The initial daily dose of warfarin was 3.2 ± 1.28 mg with a median follow-up period of 23 d (7–28). A total of 2278 PT-INR measurements were available for analysis.

**K-PD Model Evaluation** A prediction-corrected visual predictive check is shown in Fig. 1. Time courses of predicted PT-INR values were lower than those of observed PT-INR values across all measurement points. Additionally, Fig. 2 shows pc-VPC with age, body mass index, serum albumin, urea nitrogen, serum creatinine, and eGFR as independent variables. Patients aged >60 years, with body mass index ≤25 kg/m², and eGFR ≤60 mL/min/1.73 m² have a tendency toward lower predicted PT-INR. The other pc-VPCs are shown in Supplementary Fig. 1S. Additionally, the underprediction of PT-INR was consistent with a lower body surface area-unstandardized eGFR (mL/min), lower lean body weight, and lower fat-free mass, as shown in Supplementary Fig. 1S. Figure 3 shows pc-VPC stratified by the presence of concomitant drugs. Concomitant antiplatelet drugs have a tendency toward a lower predicted PT-INR.

The relationships between IPE and sampling times are shown in Fig. 4. The results of the four prior observations are nearly identical to those of all prior observations. The percentages within 20% of IPE% for 0–5 sampling times were 46, 47, 51, 56, 58, and 60%, respectively. IPE was biased in a negative direction for sampling from zero to three times. We ascertained that the improvement in the percentages within 20% of IPE% was accompanied by a higher number of Bayesian predictions. Stratification by antiplatelet use, patient age ≤60 years, body mass index >25 kg/m², and eGFR >60 mL/min/1.73 m² showed a decreasing bias in IPE, with the impact being more pronounced for age and body mass index.

**DISCUSSION**

This study revealed that the K-PD model for warfarin in Swedish patients could underpredict PT-INR in Japanese patients. This underprediction was notable in patients with renal...

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Fig. 3. Prediction-Corrected Visual Predictive Check Stratified on the Presence of Concomitant Use of Drugs

X-axis and Y-axis represent the warfarin therapy period and prediction-corrected observed and predicted values, respectively. Upper panel, stratified on the presence of concomitant use of amiodarone; lower panel, stratified on the presence of concomitant use of antiplatelet drugs. Antiplatelet drugs include low-dose aspirin, ticlopidine, clopidogrel, prasugrel, and cilostazol.
impairment and low body mass index, elderly patients, and patients using antiplatelet therapy. The prediction accuracy improved with a large number of measurement points.

The applied K-PD model included significant relevant covariates, including age and genetic variants of CYP2C9 and VKORC1.6 Generally, age has a negative correlation with S-warfarin clearance with large variability, which makes it difficult to interpret our findings.6 Age might have a strong impact on the elevation of PT-INR during warfarin treatment beyond expectations. We consider that genetic variants were the predominant reason for the dissociation between the predicted and observed PT-INR values. In addition, the influence of low body mass index on prediction accuracy was notable in the present study. Indeed, a previous study demonstrated that a small body size was associated with an increased risk of bleeding associated with warfarin therapy.14,23,24 Hence, the present study suggests that a low body mass index is an important factor in tailoring warfarin dose requirements. These findings highlight the need to construct a K-PD model that is suitable for Japanese patients who undergo warfarin therapy.

The kidneys play an important role in drug elimination. However, previous research has demonstrated that free clearance decreases with advancing chronic kidney disease stage in CYP2C9 substrates.25 Furthermore, warfarin dose requirement was correlated with creatinine clearance, adjusting for the VKORC1 genotype.26 These reports strongly support that renal function affects not only pharmacokinetics but also pharmacodynamics. Therefore, it is difficult to determine the appropriate warfarin dose requirement for patients with renal impairment. The modified K-PD model required further refinement to optimize warfarin dose requirement in patients with renal impairment, in addition to elderly patients and patients with low body mass index. Older age, lower renal function, lower body mass index, lower lean body weight, and lower fat-free mass, which were found to reduce the predictive performance in this study, are characteristics consistent with those of patients with sarcopenia. In oral anticoagulants, lean body weight was reported as a variable in direct oral anticoagulant levels in patients with sarcopenia.27 Dose–response analyses using warfarin dose and PT-INR have also reported an increased responsiveness with a decreased fat-free mass.28 The creatinine used to calculate eGFR also varies with muscle mass. Muscle strength measures, such as grip strength and short physical performance battery, and renal function measures, such as cystatin C, which are not affected by muscle mass, should be considered as potential covariates in a K-PD model for Japanese patients.

Warfarin interacts with amiodarone and N-diethyl amiodarone, the active metabolite of amiodarone, resulting in the elevation of S-warfarin concentration by inhibiting CYP2C9.29,30 This effect remains long-term because amiodarone and N-diethyl amiodarone have a long half-life. However, we could not detect it because only 9.9% of all cases were treated with amiodarone. In addition, antiplatelet medications slightly affect the prediction accuracy. Co-administration of antiplatelet medication increases the risk of bleeding due to pharmacodynamic alteration.14 In the present study, as shown in Fig. 3, there was a trend towards the underprediction of PT-INR with the concomitant use of antiplatelet agents. However, clopidogrel, one of the antiplatelet agents studied in this study, has not been found to interact with warfarin.11 The impact of each antiplatelet agent on the predictive performance needs to be investigated in the future. More than 30 algorithms to predict warfarin dose requirement did not include amiodarone as a clinical covariate, which can predict warfarin dose requirements of approximately 50%.2 Thus, we believe that concurrent medications are a clinically significant factor for warfarin dose requirements.

Several reports support that Bayesian dose optimization is useful for improving the prediction capacity of the population pharmacokinetic model.20 As the number of PT-INR measurements increased, we confirmed that the Bayesian prediction produced a better prediction capacity. Bayesian prediction using four PT-INR measurements showed that 58% of cases were within IPE ±20%, and underprediction was reduced. This result is comparable to that of the prediction using all the measurements. The K-PD model tended to underpredict PT-INR in Japanese patients. However, as shown in Fig. 4, the percentage of patients with IPE ±20% increased by Bayesian estimation, taking into account the presence of concomitant antiplatelet agents, eGFR, age, and body mass index. Espe-
cially for patients aged ≤60 years with a body mass index >25 kg/m², Bayesian estimation of two PT-INR measurements showed that about half of the patients had an IPE of ±20%. For a more accurate prediction, it would be desirable to build a K-PD model for the Japanese population, but we believe that the K-PD model reported in this study has clinical applicability. Thus, this method is valuable in the early stages of warfarin therapy introduction. Although the measurement interval of PT-INR was inconsistent, further studies are warranted to establish the best timing.

Predictions from the warfarin K-PD model in Chinese patients have been reported to overpredict maintenance doses at dosing rates above 6 mg/d.12) Because this study included patients in the induction phase of warfarin therapy, data at a daily dose of 6 mg/d or higher were observed in 4 patients (1.7%), and the relationships between the predictability and high dose could not be observed in the present study. A study of ethnic differences in the pharmacokinetics of meloxicam, which is metabolized by CYP2C9 in the same manner as warfarin, did not detect any ethnic differences in pharmacokinetics between Japanese and Chinese patients.21) Therefore, Japanese, as well as Chinese, may overpredict the maintenance dose at dosing rates above 6 mg/d in the maintenance stage. The investigation of maintenance doses in the Japanese population is a subject for future investigation.

This study had several limitations in interpreting the results. First, this was a single-center, retrospective, observational study that did not pursue all potential confounding factors. Second, we could not quantify medication adherence based on the study design. Additionally, other clinical backgrounds (e.g., actual dietary intake and cirrhosis) were not evaluated. Third, the genetic variants of CYP2C9 and VKORC1 are unknown. Therefore, we decided not to perform further analyses because we could not modify the K-PD model. Finally, the plans for warfarin dose adjustment varied. The K-PD model for warfarin in Swedish patients underpredicts PT-INR in Japanese patients with renal impairment and low body mass index, elderly patients, and patients using antiplatelet therapy, which highlights the need for a renal-function-guided K-PD model. Further studies are required to construct a model to predict warfarin dose requirements in Japanese patients.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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