

Research Article

VKORC1 and CYP2C9 Genetic Variant-Associated Warfarin Treatment Outcomes and Artificial Intelligence-Based Dosing Optimization Among Chinese Patients

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Abstract

Background: As warfarin therapy outcomes in Chinese patients can differ from those in other populations owing to differences in genotype frequencies and demographic characteristics (e.g., weight and height), this study was developed to investigate warfarin treatment patterns among Chinese patients and to propose dose optimization. **Methods:** This study recruited adults undergoing heart valve replacement surgery who received warfarin treatment. Several anticoagulation response-related parameters were measured in these patients and compared among major genotype subgroups. These data were used to construct a population-based pharmacometric model, and warfarin initiation dosing regimens were proposed using generative artificial intelligence (GAI)-assisted model simulation. **Results:** We found that those patients carrying the Vitamin K epoxide reductase complex subunit 1 (VKORC1) AA & Cytochrome P450 family 2 subfamily C member 9 (CYP2C9)*1/*1 genotype, which accounted for the majority of patients (73.3%), achieved 39% time in the therapeutic range (%TTR) within the first week of treatment, stabilizing to approximately 50% within four weeks after initiating warfarin therapy. In contrast, those patients carrying the VKORC1 AA & CYP2C9*1/*3 genotype (8.9%) exhibited more pronounced fluctuations in %TTR, while those with the VKORC1 GA & CYP2C9*1/*1 genotype (15.1%) tended to exhibit subtherapeutic %TTR. The GAI-based dosing regimen proposed in this study, consisting of higher loading doses on Days 1–5 and lower maintenance doses thereafter, was found to enable patients to achieve target international normalized ratio (INR) range within one week. **Conclusion:** As over 70% of Chinese patients have the VKORC1 AA/CYP2C9*1/*1 genotype, this means that most carry more than one VKORC1/CYP2C9 variant allele. On average, those patients with >1 VKORC1/CYP2C9 variant allele required lower warfarin doses and reached the therapeutic INR range more quickly than those with ≤1 variant allele. GAI-based approaches can provide value as a means of facilitating dose optimization based on modeling and simulation.

Keywords: generative AI; ethnicity; *in silico* modeling; *in silico* simulation; warfarin

1. Introduction

Warfarin is a classic oral anticoagulant that is widely used to treat and prevent thromboembolic disorders [1,2,3]. Although direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, edoxaban, and betrixaban, have gradually gained acceptance across multiple indications [4], warfarin remains an important option due to its long clinical history. For patients with moderate-to-severe mitral stenosis or undergoing heart valve replacements, warfarin is the recommended option over DOACs [1]. While warfarin is generally considered safe, efficient, and cost-effective, its therapeutic range is narrow, and its dosing requirements vary substantially among patients. Clinical characteristics, such as age, height, weight, co-medication, and ethnicity, together with genetic polymorphisms, can explain roughly 50% of dosing variability [5]. Therefore, for patients initiating

warfarin therapy, close monitoring of international normalized ratio (INR) values and subsequent dosing changes are essential to reach and maintain the target range for many indications.

To guide warfarin dosing, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has adopted two authoritative algorithms developed by the International Warfarin Pharmacogenetics Consortium (IWPC) and by Gage et al. [6,7]. Both algorithms were developed based on data from Western populations and predict stable warfarin doses based on the clinical and genetic characteristics of patients. The use of these dosing algorithms has allowed clinicians to achieve a higher percentage of time in therapeutic range (%TTR) while reducing adverse effects such as major bleeding, venous thromboembolism, or death in clinical trials enrolling patients receiving war-



farin for anticoagulation [8,9,10]. In a study analyzing data from the genotype-guided dosing program, dosing based on pharmacogenetic algorithms was associated with pronounced differences in anticoagulation performance among different genotypes [11]. Specifically, patients harboring ≥ 2 reduced-function Vitamin K epoxide reductase complex subunit 1/Cytochrome P450 family 2 subfamily C member 9 (VKORC1/CYP2C9) alleles reached the target therapeutic window relatively quickly. However, compared to those without these variant alleles, these patients were more likely to overshoot the therapeutic range and to exhibit an INR greater than 4, which is associated with increased bleeding risk. Additionally, the Clarification of Optimal Anticoagulation through Genetics (COAG) study found that the %TTR for African American patients receiving genotype-guided dosing was reduced compared to the clinical dosing arm [12]. This suggests that applying dosing algorithms based on data from Western patient populations may lead to variable performance across ethnicities. To help address this issue, pharmacogenetic algorithms derived from local patient populations have been developed to maximize anticoagulation efficacy while minimizing adverse effects in patients of different ethnic groups [13].

In general, Chinese patients require lower doses of warfarin than Western patients to avoid the incidence of major bleeding and intracranial hemorrhage [14]. For instance, the VKORC1 -1639 AA and CYP2C9 *1/*1 genotypes are present in at least 80 and 90% of Chinese individuals, respectively. This is in contrast with Western populations, which exhibit greater variability in terms of polymorphisms in VKORC1 (-1639 GG, AG, and AA) and CYP2C9 (*1, *2, and *3) [15]. Variants in VKORC1 influence how sensitive a patient is to warfarin, while CYP2C9 is the enzyme responsible for warfarin metabolism [16,17]. Other genetic factors such as Cytochrome P450 Family 4 Subfamily F Member 2 (CYP4F2) and Gamma-Glutamyl Carboxylase (GGCX) explain a smaller percentage of dosing variability [18,19]. In this study, we enrolled patients who were initiating warfarin after undergoing heart valve replacement surgery. VKORC1 and CYP2C9 polymorphisms were evaluated in these patients, since these two genotypes were regarded as the predominant genetic factors influencing warfarin dosing variability. The degree of INR fluctuations across different VKORC1 and CYP2C9 genotypes was analyzed in these patients. Patient data were also used to guide kinetic/pharmacodynamic (K/PD) model development, and proposed pharmacogenetics-guided initiation regimens were proposed for Chinese patients using artificial intelligence (AI)-based simulation algorithms.

2. Materials and Methods

2.1 Study Population and Procedures

Patients at two Class III, Grade A hospitals in Zhengzhou and Kaifeng in China were recruited into this study from 2023 through 2025. Inclusion criteria were as

follows: (1) age ≥ 18 years; (2) patients undergoing cardiac valve surgery and receiving warfarin for anticoagulation; (3) patients with a target therapeutic INR window of 2.0–3.0; (4) patients willing to return for scheduled follow-ups; (5) patients willing to provide written informed consent. Exclusion criteria were as follows: (1) physician-identified cognitive impairment with the potential to compromise treatment; (2) patients who had undergone transfusion within two weeks before starting treatment or who had a history of bone marrow transplantation; (3) patients who were ineligible to participate as determined by physician assessment. Warfarin doses were prescribed by clinicians based on regular INR monitoring in accordance with institutional clinical practice. Most patients were followed for up to approximately 90 days after surgery. Upon discharge, patients were given an information pamphlet, which advised avoiding eating foods such as spinach, cabbage, and broccoli that are high in vitamin K, since these may decrease the anticoagulation effect of warfarin. Patients were also advised to quit smoking and curb heavy drinking, since smoking and drinking alcoholic beverages can increase warfarin metabolism.

2.2 Data Collection and Statistical Analysis

Data collected from patients included demographic characteristics, clinical characteristics, laboratory results, and CYP2C9 and VKORC1 genotypes. Fluorescent Polymerase Chain Reaction (PCR) probes were used to detect CYP2C9 1075A>C and VKORC1 1639G>A polymorphisms. VKORC1 genotypes were categorized as GG (homozygous wild-type), GA (heterozygous mutant), and AA (homozygous mutant), while CYP2C9 genotypes were categorized as *1/*1 (homozygous wild-type), *1/*3 (heterozygous mutant), and *3/*3 (homozygous mutant). The baseline characteristics of the study participants were summarized based on stratified analyses of genetic subgroups with ≤ 1 and > 1 variant VKORC1 and CYP2C9 alleles. The time to achieve an initial therapeutic INR within the 2.0–3.0 range, rate of INR increase to first therapeutic INR, number of patients with an INR > 4 , and average daily warfarin dose (mg/day) during hospitalization were calculated. Statistical tests including Welch's two-sample *t*-test and Pearson's chi-square test were used for study analyses. Welch's *t*-test is a modification of the Student's *t*-test that does not require homogeneity of variances, making it particularly useful for pharmacogenetic studies in which observation variance may not be consistent. Pearson's chi-square test was used to assess the associations between two categorical variables based on core assumptions of random sampling and adequate expected frequencies (> 5 in most category). In addition, in order to investigate anticoagulation effects among different genotype groups, the percentages of time below, within, and above the INR therapeutic window (2.0–3.0) were calculated and plotted at various time intervals. In total, this study enrolled 146 patients under-

going heart valve replacement who received warfarin for anticoagulation treatment. While a formal statistical power calculation was not performed, this sample size was considered sufficient to capture dose/response trends in Chinese patients from typical cardiovascular surgery units in Chinese clinical settings and to support model construction by achieving successful convergence in nonlinear mixed effects modeling and providing precise estimates of model parameters (percent relative standard error (%RSE) for fixed effects <30%).

2.3 Population Modeling for Warfarin Dose/Response

2.3.1 Base Model

A K/PD structural model developed by Hamberg et al. [20] was used as a basis for model construction in our study. The major distinction between this K/PD model and traditional pharmacokinetic/pharmacodynamic (PK/PD) models is that it utilizes dose only (no pharmacokinetic PK measurements) and establishes a virtual compartment representing drug amount that is linked directly to the PD part of the model. As we did not collect plasma PK data in our study, parameters in the PK component were fixed to those from the PK model for warfarin treatment reported by Ohara et al. [21] based on plasma concentrations and INR data from 99 Chinese patients. In our model, as shown in Fig. 1, only S-warfarin within the racemic mixture was a driver of the anticoagulation response. The PK component included the following 1-compartment structure as shown in Eqns. 1,2. The initial condition for dA/dT was 0. K_a is the absorption rate constant for oral absorption in the model.

$$k_e = \frac{CL}{V} \quad (1)$$

$$\frac{dA}{dT} = -k_e \cdot A \quad (2)$$

where A represents the amount of S-warfarin (which is one-half of the full dose of racemic warfarin) in the central compartment, V is the volume of distribution, and CL is S-warfarin clearance. The following covariates in PK were also included in the Ohara PK model: $CL(S) \text{ L/h} = 0.24 \times 0.543^{CYP2C9*3} \times (BSA_{\text{individual}}/1.74)^{2.14}$, with $CYP2C9*3$ being 0 in patients with $CYP2C9*1/*1$ and $CYP2C9*3$ being 1 in patients with the $CYP2C9*1/*3$ genotype. $BSA_{\text{median}} = 1.74 \text{ m}^2$, and $BSA_{\text{individual}}$ is calculated as $0.007184 \times (HT^{0.725}) \times (WT^{0.425})$ (Du Bois formula, body surface area BSA in m^2 , height HT in cm, and weight WT in kg). Parameters in the PK component shown above were fixed in accordance with the original publication [21].

Equations for the PD component are shown below, with the drug effect being driven by the dosing rate DR , which represents the amount of S-warfarin (A) in the dos-

ing compartment per unit of time (Eqn. 3). Drug effect EFF itself is shown by the maximum drug effect (E_{max}) model in Eqn. 6, with parameters such as E_{max} , γ , and EDK_{50} in addition to DR . E_{max} is the maximum inhibition of coagulation factors by S-warfarin, which is fixed to 1. The shape factor γ is used as an exponent for the terms DR and EDK_{50} . EC_{50} (Effective Concentration 50%) is the sum of EC_{50} for the VKORC1 G and A alleles. EDK_{50} is equal to the product of CL and EC_{50} , representing the dose rate leading to 50% inhibition.

$$DR = k_e \cdot A \quad (3)$$

$$EC_{50} \propto f(EC_{50}^G + EC_{50}^A) \text{ or } EC_{50} \propto f(EC_{50}^G + EC_{50}^A) \text{ or } EC_{50} \propto f(EC_{50}^A + EC_{50}^A) \quad (4)$$

$$EDK_{50} = CL \cdot EC_{50} \quad (5)$$

$$EFF = \frac{E_{\text{max}} \cdot DR^\gamma}{EDK_{50}^\gamma + DR^\gamma} \quad (6)$$

To characterize delay in the warfarin dose/response relationship, a three-compartment transduction chain was used as shown in Eqns. 7,8, where the number of compartments (n) equals 3 and mean transit time (MTT) represents the mean transit time across the transduction chain.

$$\frac{dC1_1}{dT} = (1 - EFF) \cdot \frac{n_{C1}}{MTT_{C1}} - C1_1 \cdot \frac{n_{C1}}{MTT_{C1}} \quad (7)$$

...

$$\frac{dC1_3}{dT} = C1_2 \cdot \frac{n_{C1}}{MTT_{C1}} - C1_3 \cdot \frac{n_{C1}}{MTT_{C1}} \quad (8)$$

The INR response is represented by Eqn. 9, where INR_{baseline} represents the baseline INR of each patient and INR_{max} (maximum INR response) is fixed to 20.

$$\widehat{INR} = INR_{\text{baseline}} + INR_{\text{max}} \cdot (1 - C1_3) \quad (9)$$

2.3.2 Covariate Model

Our base model retained covariates included by Ohara et al. [21] and Hamberg et al. [22], which were used as

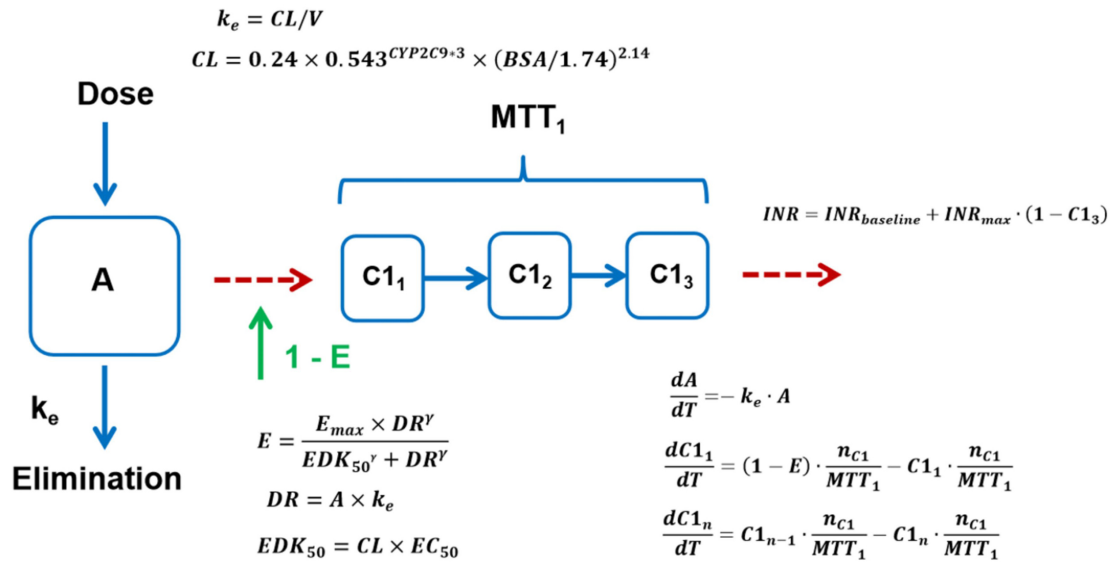


Fig. 1. Schematic representation of the basic kinetic/pharmacodynamic (K/PD) model structure used to characterize the warfarin dose/response relationship. A = the amount of S-warfarin in the central compartment; V = volume of distribution; CL = the clearance of S-warfarin; $k_e = CL/V$; $BSA_{individual} = 0.007184 \times (HT^{0.725}) \times (WT^{0.425})$ (Du Bois formula, BSA in m^2 , HT in cm , and WT in kg); $CL(S)$ $L/h = 0.24 \times 0.543^{CYP2C9*3} \times (BSA_{individual}/1.74)^{2.14}$, where $CYP2C9*3 = 0$ in patients with the $CYP2C9*1/*1$ genotype and $CYP2C9*3 = 1$ in patients with the $CYP2C9*1/*3$ genotype, $BSA_{median} = 1.74 m^2$; E = drug effect; DR = dosing rate, the amount of S-warfarin (A) in the dosing compartment per unit of time; $E_{max} = 1$, the maximum degree of inhibition of coagulation factors by S-warfarin; EC_{50} = the sum of combinations of EC_{50} for $VKORC1$ G and A alleles; EDK_{50} = dose rate leading to 50% inhibition, equal to the product of CL and EC_{50} ; γ = shape factor; MTT = the mean transit time across the transduction chain; INR = response in the model; $INR_{baseline}$ = baseline INR of each patient; $INR_{max} = 20$. BSA , body surface area; HT , height; $CYP2C9$, Cytochrome P450 family 2 subfamily C member 9; EC_{50} , Effective Concentration 50%; MTT , mean transit time; INR , international normalized ratio.

the basis for model construction. Namely, the base model includes covariates for $CYP2C9*3$ and BSA on $CL(S)$ as in the original PK model structure outlined by Ohara et al. [21]. With respect to PD parameters, the base model included $VKORC1$ and $CYP2C9$ as in the original model by Hamberg et al. [22]. In addition, stepwise forward inclusion and backward elimination covariate searching was performed to identify significant covariates in the model. The covariates that were considered for potential effects on PK ($C(L)$ and V) and PD parameters (EC_{50}) are shown in **Supplementary Table 1**. The significance threshold for forward inclusion steps was $p < 0.05$, while that for the backward elimination steps was $p < 0.01$, assuming a χ^2 distribution for the $-2\log$ likelihood objective function.

2.3.3 Statistical Model for Random Effects

An exponential error model was used to account for interindividual variability (IIV) as shown in Eqn. 10.

$$P_{ij} = \theta_j \exp(\eta_{ij}) \quad (10)$$

A Log-additive error model was used to account for residual effects, as shown in Eqn. 11.

$$\text{LOG}(INR) = \text{LOG}(\widehat{INR}) + \varepsilon_{ij} \quad (11)$$

2.3.4 Model Evaluation

Model performance was evaluated using goodness-of-fit (GOF) plots comparing observed versus individual predictions for INR , observed versus population predictions for INR , CWRES (conditional weighted residuals) INR versus Time (Day), and CWRES versus population prediction for INR . A visual predictive check (VPC) approach was used to evaluate whether the model, as a whole, adequately described the central tendency and variability of the observed data over time. Individual INR predictions versus Time (Day) plots were used to evaluate how well the model captured the observed INR data at the individual patient level.

2.3.5 Software

The K/PD model used to characterize warfarin dose/response in Chinese patients in this study was modeled using the NONMEM nonlinear mixed effects modeling software (version 7.5, ICON Development Solutions, Ellicott, Maryland, USA). Data analysis and plotting were performed using the gtsuammary and ggplot2 packages in

R (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria).

2.4 GAI-Assisted Optimization of Warfarin Dosing Regimen

2.4.1 Overall Approach

First, a K/PD model was constructed based on dosing and INR response data from 146 Chinese patients receiving warfarin for anticoagulation following heart valve replacement surgery. The final K/PD model was then translated into R code using the *mrgsolve* package (see example code in **Supplementary Material**). The example simulation and optimal dose search code written in Python was added in **Supplementary Materials** as well. Based on this model, a generative artificial intelligence (GAI) system was used to perform simulations and optimize warfarin dosing regimens for the three most common VKORC1/CYP2C9 genotype combinations in the Chinese population (VKORC1 1639 AA & CYP2C9*1/*1, VKORC1 1639 AG & CYP2C9*1/*1, and VKORC1 1639 AA & CYP2C9*1/*3). The following example command prompt was given to the large language model (LLM) for task execution:

*“Based on the mrgsolve simulation code uploaded, optimize dosing for someone with the following covariates: HT = 165 cm, WT = 65 kg, CYP2C9 = *1/*1, VKORC1 = AA, INR_BASE = 1. Output the key parameters in the simulation, the daily doses, and INR.”*

Please note that the LLM is separate from the pharmacometric model and numerical optimization algorithms and that here the LLM did not directly generate individualized doses. The final dose recommendations were determined by the validated K/PD model and deterministic numerical optimization algorithms, while the LLM primarily served as an intelligent workflow controller to orchestrate the optimization workflow.

2.4.2 Technical Details

A GAI system was leveraged to develop a controllable and verifiable professional decision-making module through the implementation of a highly engineered workflow, allowing for behavioral alignment and targeted knowledge transfer from general generation to professional reasoning. This technical approach was divided into two core stages, fully leveraging the generative capabilities of GAI systems while mitigating the generalization bias of general models to enable the formulation of intelligent drug delivery solutions.

(1) Workflow Architecture Design and Model Transfer

We employed Qwen2.5-72B-Instruct as the core base model for natural language interpretation, clinical feature extraction, and workflow orchestration. To mitigate the inherent hallucination risks and generalization bias associ-

ated with general large language models, our system introduces the core concept of an “Engineered AI Workflow”, establishing a strict boundary between natural language processing and quantitative pharmacological calculation. Through this highly engineered design, the system is able to successfully achieve a targeted transition from a general-purpose generative model to a domain-specific pharmacological module. Within this framework, the LLM is separate from the pharmacometrics model and numerical optimization algorithms and does not directly generate dose predictions; rather, functioning as an intelligent workflow controller of a multi-node autonomous pipeline, it orchestrates the operation of the entire closed-loop engineered framework.

Under the control of this intelligent controller, the workflow operates as a closed-loop sequential architecture that progresses from frontend patient feature extraction and intent recognition, through the mid-end scheduling of optimal dose searching and simulation modeling, and concludes with backend automated parameter consistency verification and standardized result formatting. This continuous flow forms a complete and rigorous intelligent decision-making chain.

In the frontend phase, the system utilizes the GAI model to deeply parse complex, unstructured clinical dialogues, effectively decoupling patient-specific clinical covariates (e.g., height, weight, baseline INR, and VKORC1/CYP2C9 genotypes) from the physician’s clinical intent. Beyond processing standard inputs, the system employs intent recognition for dynamic task routing: when identifying a task as a dynamic dose adjustment rather than an initial calculation, the workflow directs the model to automatically retrieve and load historical dosing data from existing CSV (Comma-Separated Values) files. Upon accurately extracting parameters and intents, the workflow transitions to the mid-end execution phase. Rather than executing rigid, static code templates, the GAI functions as an intelligent code-adaptor. It dynamically parameterizes and restructures the underlying Python and R scripts by directly mapping the extracted multidimensional clinical covariates into the computational logic. Through this dynamic adaptation mechanism, the system ensures that the customized Python module (WarfarinDoseOptimizer) for optimal dose searching and the R scripts for simulation modeling are highly customized for each unique patient case before execution. Throughout this process, the GAI manages the execution sequence and data flow, providing the system with the flexibility to handle complex clinical contexts without interfering with the mathematical rigor of the underlying K/PD differential equations.

Subsequently, in the backend phase, the workflow integrates automated closed-loop verification and result formatting mechanisms to ensure the safety and utility of the final outputs. Utilizing conditional branching and controlled Application Programming Interface (API) invocations, we

embedded an automated parameter consistency check node (`is_consistent`) at the system's foundational level. This node algorithmically cross-validates the initial natural language inputs against the parameters actually received by the backend mathematical engine; if parameter drift or missing variables are detected, the system immediately triggers an interception mechanism and halts execution, actively preventing erroneous outputs. Finally, recognizing that the optimal dosing metrics and simulation charts outputted by the mid-end's iterative dose search and modeling process are inherently fragmented and difficult to review efficiently, the workflow introduces dedicated review nodes. These nodes utilize the GAI to integrate the verified optimal dose results and simulation plot Uniform Resource Locator (URLs) into a strictly structured and standardized format for intuitive clinical inspection. By actively filtering out underlying code execution logs and debugging information, this framework effectively translates backend numerical computations into an accessible, clear, and fully traceable professional medical decision support output.

(2) Algorithmic Realization of the Hybrid LLM + K/PD Closed-Loop Optimization

Breaking away from traditional empirical estimations, the system constructs a hybrid LLM-K/PD closed-loop optimization algorithm by deeply integrating the logical orchestration capabilities of large language models with the deterministic computations of a quantitative pharmacological engine. This algorithm is designed to precisely compute individualized 21-day warfarin dosing regimens (divided into a 5-day loading phase and a 16-day maintenance phase), utilizing numerical solutions of ordinary differential equations to replace conventional trial-and-error methods, thereby enabling scientific and mathematically rigorous dosing decisions.

Driven by the intelligent controller, the system iteratively searches for and isolates the optimal dose combination through three distinct phases:

(2.1) Pharmacokinetic/Pharmacodynamic Simulation: Using the parsed structured patient parameters, the system initializes the K/PD model governed by differential equations—solved numerically via the Runge-Kutta RK45 method—to simulate daily INR time series.

(2.2) Iterative Dose Search Strategy: To stabilize the INR within the narrow target therapeutic window of 2.0–3.0 within one week of treatment initiation, a strict two-step numerical search strategy is deployed across a candidate space of valid scored tablet fractions (i.e., the recommended doses are divisible by 1/8th of a 2.5 or 3 mg tablet, which is the commonly available strength for warfarin in Chinese clinics):

Forward-Searching for Optimal Loading Dose (`find_loading_dose`): A forward-searching algorithm identifies the optimal 5-day loading dose to accelerate INR elevation toward 3.0 by Day 5. To prevent bleeding risks, candidate doses that cause a predicted INR >3.0 on Days 5

or 6 are immediately rejected, and the upper search bound is reduced accordingly.

Bisection Search for Optimal Maintenance Dose (`bisection_search`): A binary search is applied across Days 6–21 to determine the maintenance dose that achieves an ideal target median INR of 2.5. The algorithm evaluates the simulated trajectory by computing a compound objective score:

$$\text{Score} = \text{DeviationPenalty} + 2 \times \sigma_{\text{INR}} + 5 \times |\mu_{\text{INR}} - 2.5|$$

where severe penalty weights ($\times 20$) are assigned to any INR excursion below 2.0 or above 3.0, σ_{INR} represents INR fluctuation stability (standard deviation), and μ_{INR} represents the mean maintenance INR. The search dynamically narrows the bounds until it isolates the dose that minimizes the overall score without overshooting.

(2.3) Clinical Safety Verification and Transition: Each optimization iteration undergoes strict logical and safety checks. If drug accumulation causes a residual overshoot tendency on Day 6 (INR >3.0), the algorithm triggers an automated transition-dose strategy—stepping down the Day 6 dose by one clinical increment to ensure a smooth trajectory into the maintenance phase—or rejects the combination entirely. These verified numerical results are subsequently processed by the workflow's backend review nodes for final clinical formatting.

Regarding the complete optimization workflow and the specific AI scripts used in this study, the underlying framework—specifically the prompt engineering for the core base model (Qwen2.5-72B-Instruct) functioning as the “intelligent controller”, and the precise orchestration of the “multi-node autonomous pipeline” (including frontend intent recognition, dynamic task routing, and backend automated parameter consistency verification)—involves strict confidentiality restrictions, and we are currently unable to make them fully open-source. Nevertheless, the provided representative Python optimization scripts and R simulation codes should be sufficiently detailed to allow readers to fully understand the core mechanisms of our “quantitative pharmacological engine” and replicate the PK/PD-based dose optimization process in their own computing environments.

3. Results

3.1 Participant Characteristics

In total, 146 eligible patients undergoing heart valve replacement surgery were invited to participate in this study. The mean age of the enrolled participants was 58, and 42% of patients were female (Table 1). The genotype distribution for VKORC1 (1639G>A) in this population was 3/23/120 (GG/GA/AA), while that for CYP2C9*3 (1075A>C) was 131/14/1 (*1/*1, *1/*3, *3/*3). As shown in **Supplementary Fig. 1**, 51.7% of participants underwent

Table 1. Baseline and anticoagulation characteristics among enrolled patients.

Characteristics	Overall N = 146	Genetic subgroup		<i>p</i> -value ¹
		>1 Variant N = 122	≤1 Variant N = 24	
Age (yr), Mean ± SD	58 ± 14	58 ± 15	58 ± 12	0.93
Gender, n (%)				0.36
Female	61 (42%)	53 (43%)	8 (33%)	
Male	85 (58%)	69 (57%)	16 (67%)	
WT (kg), Mean ± SD	65 ± 14	64 ± 13	68 ± 16	0.33
HT (cm), Mean ± SD	166 ± 8	166 ± 8	169 ± 8	0.12
Smoking, n (%)	20 (14%)	17 (14%)	3 (13%)	0.85
Hemoglobin (g/L), Mean ± SD	133 ± 17	133 ± 17	132 ± 16	0.83
Creatinine (μmol/L), Mean ± SD	71 ± 33	70 ± 35	73 ± 19	0.53
Alanine transaminase (ALT) (U/L), Mean ± SD	30 ± 30	31 ± 33	24 ± 11	0.058
Platelet count (×10 ⁹ /L), Mean ± SD	191 ± 49	190 ± 50	197 ± 44	0.55
Aspartate aminotransferase (AST) (U/L), Mean ± SD	30 ± 22	31 ± 23	25 ± 12	0.092
Glomerular filtration rate (GFR) (mL/min), Mean ± SD	101 ± 34	102 ± 35	99 ± 30	0.62
Baseline INR, Mean ± SD	1.17 ± 0.25	1.18 ± 0.26	1.09 ± 0.17	0.039
Setting of first therapeutic INR (n = 138), n (%)				0.001
Inpatient	100 (72%)	92 (77%)	8 (42%)	
Outpatient	38 (28%)	27 (23%)	11 (58%)	

¹ Welch's Two Sample *t*-test; Pearson's Chi-squared test. SD, standard deviation; WT, weight.

tricuspid valvuloplasty, while 15–17% of patients each underwent mitral valvuloplasty, biological aortic valve replacement, mechanical mitral valve replacement, and mechanical aortic valve replacement. With respect to concomitant medications (**Supplementary Fig. 2**), above 95% of participants were taking antihypertensives and heart failure medications, while 23.1% were taking antiarrhythmics, 21.8% were taking statins, and 18.4% were taking antiplatelet medications.

3.2 Anticoagulation Responses Among Genetic Subgroups

As shown in Table 2, the time needed to achieve a therapeutic INR differed significantly between genetic subgroups, with averages of 8.7 vs. 13.7 days for those with >1 and ≤1 variant alleles, respectively. Daily warfarin dose during hospitalization also differed significantly, as patients with ≤1 variant allele had higher average doses compared to those with >1 variant allele (3.69 vs. 2.91 mg/day), shown in Fig. 2 and Table 2. For patients harboring the VKORC1 AA & CYP2C9*1/*1 genotype, %TTR rose to about 39% within the first 7 days and stabilized at approximately 50% within four weeks after initiating warfarin therapy (Fig. 3, Ref. [23]). For patients with the VKORC1 AA & CYP2C9*1/*3 genotype, however, greater fluctuations in %TTR were noted. For patients with the VKORC1 GA & CYP2C9*1/*1 genotype, %TTR rose slowly to around 10% on day 7 and then steadily climbed to 33% on days 26–28.

3.3 Model Building for Warfarin Dose/Response in Chinese Population

Additional covariates were tested using a stepwise selection process (**Supplementary Table 1**). The estimated final parameters are shown in Table 3 (Ref. [21]). In addition to the covariate effect of BSA and CYP2C9*3 on S-warfarin clearance [CL(S)] as retained in the Hamberg et al. [22] model, our final K/PD model included the following covariates: the effect of BSA on V in the PK component, the effect of Vitamin K on INR, and the effect of statins on the EC₅₀ in the PD component. PK parameters including CL(S), V, Ka, and the covariate effects of BSA and CYP2C9*3 on CL(S) were established based on a previously published population model [21]. As shown in **Supplementary Fig. 3**, reasonable goodness-of-fit (GOF) plots were generated for these covariates. Furthermore, both the individual INR prediction profiles (**Supplementary Fig. 4**) and visual predictive check (VPC) (Fig. 4) suggested that the final K/PD model performed reasonably well when capturing the observed INR response profiles of study participants.

3.4 GAI-Assisted Optimization of Pharmacogenetics-based Warfarin Dosing

Based on the final K/PD model, a GAI system was used to optimize a pharmacogenetics-based dosing regimen for a typical Chinese individual who is 1.65 m tall and weighs 65 kg harboring the most common VKORC1 and CYP2C9 genotypes: VKORC1 1639 AA/CYP2C9*1/*1, VKORC1 1639 AG/CYP2C9*1/*1, and VKORC1 1639

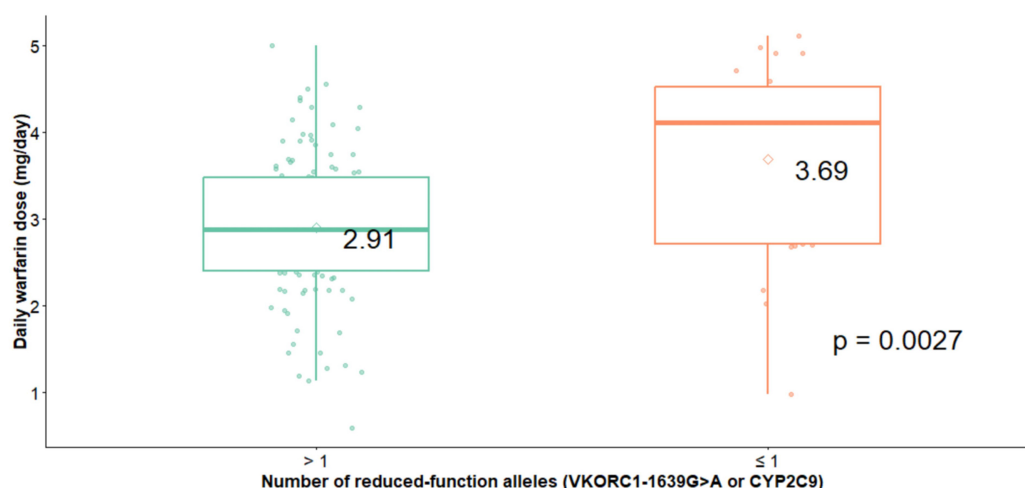


Fig. 2. Daily warfarin dose distributions during hospitalization among study participants in different genetic subgroups. Patients were stratified into two groups based on whether they harbor >1 or ≤1 reduced-function alleles (VKORC1 1639G>A or CYP2C9). In the boxplot, the rectangular box (interquartile range, IQR) represents the middle 50% of the data. The bottom edge is the 25th percentile (Q1), and the top edge is the 75th percentile (Q3), while the median dose for each group is represented by a horizontal line. The whiskers from the top and bottom of each box extend to the highest and lowest values within 1.5 times the IQR.

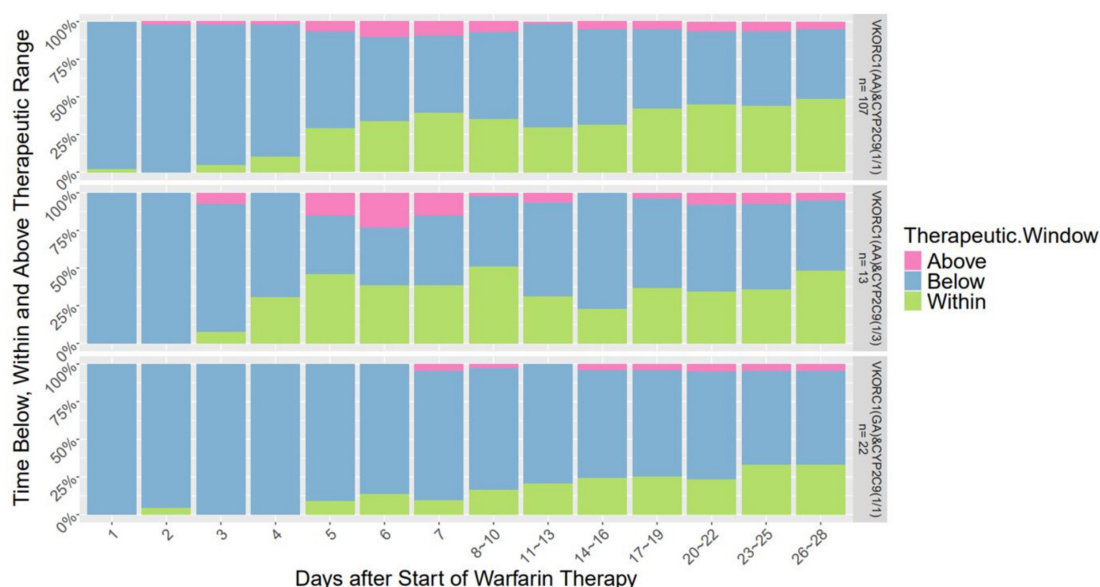


Fig. 3. Percentage of time in the target INR therapeutic range (as calculated using the Rosendaal method [23]) for study participants. Time within the target INR range (2–3; green), below this range (<2; blue), and above this range (>3; red) is shown for patients with the following genotypes: VKORC1 AA & CYP2C9*1/*1 (top panel), VKORC1 AA & CYP2C9*1/*3 (middle panel), and VKORC1 GA & CYP2C9*1/*1 (lower panel).

AA/CYP2C9*1/*3. The recommended dosing for these patient populations is shown in Table 4. As shown in **Supplementary Fig. 5**, typical Chinese individuals receiving the recommended dosing regimen were expected to reach the target INR range of 2 to 3 within one week. In contrast with these recommendations, the dose ranges of expected maintenance doses found on the FDA (food and drug administration)-approved prescription label for COUMADIN® (warfarin sodium) are 3–4, 5–7, and 0.5–2

mg for the VKORC1 1639 AA & CYP2C9*1/*1, VKORC1 1639 AG & CYP2C9*1/*1, and VKORC1 1639 AA & CYP2C9*1/*3 genotypes, respectively [24].

4. Discussion

In recent years, the use of DOACs has become increasingly common across multiple indications, including atrial fibrillation. Nevertheless, warfarin remains an important option under current clinical guidelines, especially

Table 2. Comparison of anticoagulation response among different patient genotypes.

Characteristics	Overall N = 146	Genetic subgroup		<i>p</i> -value ¹
		≤1 Variant N = 24	>1 Variant N = 122	
Time to first therapeutic INR (days) ² , Mean ± SD (standard deviation)	9.3 ± 5.3	13.7 ± 7.1	8.7 ± 4.8	0.018
Rate of INR increase ² (INR/day), Mean ± SD	0.16 ± 0.10	0.13 ± 0.15	0.17 ± 0.09	0.36
Patients with an INR >4, n (%)	22 (15%)	2 (8.3%)	20 (16%)	0.31
Daily warfarin dose during hospitalization (in mg), Mean ± SD	3.04 ± 0.91	3.69 ± 1.11	2.91 ± 0.81	0.003
TTR (30 days), Mean ± SD	0.30 ± 0.19	0.17 ± 0.17	0.33 ± 0.19	<0.001

¹Welch's Two Sample *t*-test; Pearson's Chi-squared test; ²Among the 146 patients, a total of 128 patients achieved therapeutic INR within the first 30 days of therapy, consisting of 15 patients with ≤1 variant allele and 113 patients with >1 variant allele. TTR, time in the therapeutic range.

Table 3. Parameter estimation for the final K/PD model. Kinetic parameters including CL(S), V, K_a, and the covariate effects of BSA and CYP2C9*3 were fixed based on estimates from a population PK/PD model in Chinese patients previously published by Ohara et al. [21].

Group	Parameter	Estimate	RSE (%)	ETA Shrinkage SD based (%)
PK Parameters	CL(S) [L/h]	0.24 (FIX)	-----	-----
	Effect of BSA on CL(S)	2.14 (FIX)	-----	-----
	Effect of CYP2C9*3 on CL(S)	0.543 (FIX)	-----	-----
	V [L]	13.8 (FIX)	-----	-----
	Effect of BSA on V	2.38	27.1	-----
	K _a [1/h]	2 (FIX)	-----	-----
	E _{max}	1 (FIX)	-----	-----
PD Parameters	γ	1.44	5.3	-----
	EC ₅₀ per VKORC1 G allele (mg/L)	3.05	20.6	-----
	EC ₅₀ per VKORC1 A allele (mg/L)	1.09	13.4	-----
	MTT1 [h]	30.8	10.0	-----
	INRMAX	20 (FIX)	-----	-----
	Effect of Vitamin K on INR	0.896	0.5	-----
	Effect of Statins on EC ₅₀	0.742	11.3	-----
IIV	<i>KDE (CL/V)</i>	0.233	41.6	43.5
	<i>EC₅₀</i>	0.187	15.6	12.9
RES (log-additive)	<i>INR</i>	0.218	1.0	5.48

K/PD, kinetic/pharmacodynamic; BSA, body surface area; PK/PD, pharmacokinetic/pharmacodynamic; RSE, Relative Standard Error; FIX, parameter fixed; IIV, interindividual variability.

Table 4. GAI-Optimized pharmacogenetics dosing regimen based on the final K/PD model for a typical Chinese individual who is 1.65 m tall and weighs 65 kg.

Genotypes	Recommended Dose (mg/day)	
	Days 1–5	Days 6–21
VKORC1 1639 AA & CYP2C9*1/*1	5.625	4.125
VKORC1 1639 AG & CYP2C9*1/*1	10.0	8.125
VKORC1 1639 AA & CYP2C9*1/*3	4.125	2.25

To support convenient dose adjustments, the recommended doses are divisible by 1/8th of a 2.5 or 3 mg tablet, which is the commonly available strength of warfarin in Chinese clinics. GAI, generative artificial intelligence.

for patients with mechanical heart valves or moderate-to-severe mitral stenosis [1,25]. Previously, our group has

compared the relative clinical utility of Western and Chinese genotype-guided dosing algorithms for Chinese popu-

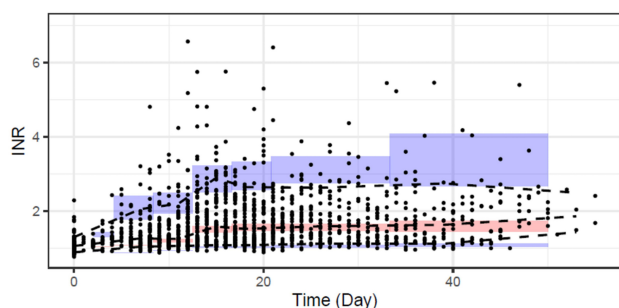


Fig. 4. Visual predictive check (VPC) for INR versus time based on the final K/PD model. Black dots = observations; black dashed lines = 80% interval and median of the observations; red shaded area = 95% confidence interval (CI) of the median prediction; blue shaded area = 95% CI of the 10th and 90th prediction interval.

lations [26,27,28], using algorithms developed by Gage et al. [7] and the IWPC as representative Western algorithms [6]. We have found that dosing recommendations based on Chinese dosing algorithms tended to be lower than those derived from these two representative Western algorithms when evaluating Chinese patient populations [26]. This deviation in predictions was in the negative direction and was most pronounced for younger individuals with lower body weight. We also previously evaluated the predictive performance of 10 dosing algorithms from 8 countries, comparing predicted maintenance doses against measured doses in Chinese patients who were initiating warfarin after heart replacement [28]. These analyses revealed that, for Chinese cohorts, region-specific algorithms based on Asian data performed better than international models (e.g., the IWPC/Gage models recommended by CPIC). This again highlights the need to consider ethnic sensitivity in dosing requirements especially for a drug with narrow therapeutic index such as warfarin.

In this study, we enrolled 146 eligible patients undergoing heart valve replacement procedures. As expected from previous reports in Asian cohorts, most patients harbored the VKORC1 AA/CYP2C9*1/*1 genotype (107/146). A total of 138 out of 146 patients were able to reach the therapeutic INR range of 2–3, and 77% (92/119) of those with >1 reduced-function VKORC1/CYP2C9 variant allele achieved this therapeutic range while in the inpatient setting, as compared to just 42% (8/19) of those patients with ≤1 variant allele (Table 1). Patients with >1 variant allele were able to achieve the target therapeutic range more quickly than those with ≤1 variant allele (8.7 vs. 13.7 days), while receiving lower daily warfarin doses during hospitalization (2.91 vs. 3.69 mg). While patients with >1 variant allele achieved higher %TTR while in the inpatient setting (26% vs 8%), this group also exhibited a higher risk of overshooting the therapeutic window (INR >4) compared to those with ≤1 variant allele

(16% vs. 8.3%). When patients were stratified based on specific genotypes, those harboring the VKORC1 AA & CYP2C9*1/*1 genotype stabilized at a %TTR of approximately 50% after four weeks of therapy, while those harboring the VKORC1 GA & CYP2C9*1/*1 genotype were more likely to undershoot the therapeutic range, stabilizing at a %TTR of approximately 33%. Patients harboring the VKORC1 AA & CYP2C9*1/*3 genotype exhibited greater variability, with a %TTR peaking at 46% on day 5 (first peak), decreasing to 38% on days 6–7, again peaking at 51% on days 8–10 (second peak), dropping to 23% on days 14–16, and gradually increasing to 48% on days 26–28 (third peak). Based on these INR response patterns, in the majority of Chinese patients harboring the VKORC1 AA/CYP2C9*1/*1 genotype, who accounted for 73.3% (n = 107/146) of this study population, the %TTR achieved within one week of initiating warfarin therapy was 40% before stabilizing at 40–50% after four weeks. For patients harboring the VKORC1 GA/CYP2C9*1/*1 genotype (15.1%, n = 22/146), in contrast, there was a general trend toward underdosing, as the %TTR remained under 10% during the first week and gradually increased to about 33% after four weeks. For those individuals with the VKORC1 AA & CYP2C9*1/*3 genotype (8.9%, n = 13/146), although a %TTR of 40–50% was achieved after the first week, greater variability was observed over time, as this group was most sensitive to warfarin anticoagulation. Even so, these results demonstrate that the current dosing approach in typical Chinese hospital settings was sufficient to effectively and stably achieve a therapeutic level of anticoagulation in the majority of patients, who harbor the VKORC1 AA/CYP2C9*1/*1 genotype. Our results are in line with the %TTR values reported in other studies. Kim et al. [29], for instance, reported a mean %TTR of 34% based on data from 11,835 patients who received warfarin at Seoul National University, while Zhu et al. [30] reported a %TTR of 48.5% among 394 Chinese patients receiving warfarin. As shown in Fig. 3, the percentage of time within or below the therapeutic INR 2–3 in our study cohort was at least 90%. In our experience, this phenomenon occurs due to concern among physicians about the potential for over-anticoagulation leading to increased bleeding risk. In general, Asian populations reportedly present with greater thromboembolic protection at lower INR values as compared with Caucasian populations and thus may require lower initiation and maintenance doses of warfarin [31].

The data in this study were further used to develop a population pharmacometric model to capture warfarin treatment response among Chinese patients. As shown in Table 3, PK parameters were fixed based on a previously reported population PK/PD model in Asians wherever possible [21], while PD parameters such as γ , EC_{50} , and MTT were estimated. Covariate estimates revealed that BSA was positively correlated with the volume of distribution (V), while statin use was associated with a decrease in EC_{50} , and vita-

min K was associated with overdose instances with a spike in INR. GOF plots, individual INR prediction profiles, and VPC all confirmed reasonable model fitting and predictive performance (**Supplementary Figs. 3,4, Fig. 4**).

AI tools are increasingly positioned to fundamentally transform how healthcare is managed, delivered, and analyzed. With respect to genomics and personalized medicine, the holistic use of digital tools, including AI, has the potential to help us better analyze complex genomic data and promises to revolutionize disease prevention, diagnosis, and treatment [32]. Established, clinically useful single-gene predictors, such as CYP2C19 for antiplatelet therapy and VKORC1/CYP2C9 for warfarin dosing, form the foundation of current pharmacogenomic practice. Current AI-driven approaches include efforts to expand on traditional, single-gene pharmacogenomics approaches by using Polygenic Risk Scores (PRS) and Machine Learning (ML) to aggregate the effects of many genetic variants in an effort to provide a more comprehensive picture of heritable disease risk [33]. In this study, a GAI approach was employed to recommend a pharmacogenetic-based dosing regimen for warfarin use in Chinese patients. After initially constructing a K/PD model based on the dosing and INR response data from 146 Chinese patients receiving warfarin for anticoagulation following heart valve replacement surgeries, GAI was used to optimize a pharmacogenetic dosing regimen for typical Chinese individuals with the most common VKORC1 and CYP2C9 genotypes (Table 4). Based on model simulations for typical Chinese individuals, patients receiving the recommended dosing regimen were expected to reach the therapeutic INR window within one week of initiating warfarin therapy. Importantly, the GAI-recommended maintenance doses were all close to the expected dose range found on the FDA-approved prescription label for COUMADIN® (warfarin sodium) [24]. To further enhance the translational significance of the study, multicenter prospective validation of the recommended dosing regimen needs to be performed before routine clinical implementation. The importance of multicenter prospective validation of warfarin dosing algorithms cannot be overstated as this accounts for real-world clinical complexities and provides clinical evidence of the performance of the dosing algorithms. Examples of landmark multicenter, prospective trials are the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial and the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, both of which provide evidence on whether genotype-guided dosing of warfarin could improve anticoagulation control in the Western populations [8,12].

5. Limitations

This study only enrolled patients who had undergone heart valve replacement surgeries. The two major indications for warfarin use in China are atrial fibrillation (AF) and heart valve replacement. For patients undergoing heart

valve replacement, in contrast, warfarin remains the recommended option over DOACs [34,35], explaining why this population was the focus of the present study. However, there is no reason to assume these findings are not generalizable to other warfarin-treated populations such as AF patients.

While our GAI-based pharmacometric system holds promise as a means of mitigating the potential for “hallucinations” attributed to large language models when seeking to optimize dosing regimens, two primary limitations must be noted. First, with respect to model dependency and covariate sensitivity, the accuracy of the individualized dose recommendations is fundamentally bounded by the structural assumptions of the underlying K/PD model and the precision of patient-specific input covariates. Although the baseline model was derived from a rigorous analysis of 146 Chinese patients who had undergone heart valve replacement, extrapolating these results to those with extreme body mass index (BMI) values, severe hepatic/renal impairment, or rare genetic polymorphisms beyond the three main VKORC1/CYP2C9 genotypes evaluated herein may introduce prediction variance. Second, this model requires prospective real-world clinical validation. Although our system was validated through comprehensive retrospective simulations and successfully replicated clinical dosing curves for major genotype combinations, *in silico* simulations cannot fully capture the dynamic behavioral and physiological complexities of real-world patient management (e.g., dietary vitamin K intake fluctuations, concomitant medication interactions, and poor patient compliance). Therefore, multicenter, prospective randomized controlled clinical trials are necessary to conclusively establish the clinical efficacy and safety of this GAI-assisted decision module before widespread clinical adoption.

In addition, there are practical limitations to implementing GAI-assisted dosing in routine clinical practice, including the need to appropriately validate a model capable of accurately characterizing warfarin dose/response relationships in the intended population. After a final validated model has been established, the GAI system will be able to perform the necessary simulations to make dosing recommendations based on clinical and genetic inputs for a given patient, while also taking into account INR monitoring data during the dosing initiation period. To support widespread uptake, this model would also benefit from the development of a convenient smartphone application or similar platform to allow for reliable use when querying dosing recommendations.

6. Conclusions

In summary, Chinese patients with >1 variant VKORC1 and CYP2C9 alleles require lower warfarin doses and achieve therapeutic INR values more quickly than those with ≤1 variant allele, with an average time to first therapeutic INR of 8.7 versus 13.7 days for these populations,

respectively. When grouped according to genotype, those with the VKORC1 AA & CYP2C9*1/*1 genotype, which accounted for the majority of patients (73.3%), achieved 39% in %TTR within the first week and stabilized at approximately 50% within four weeks after initiating warfarin. In contrast, patients harboring the VKORC1 AA & CYP2C9*1/*3 genotype (8.9%) exhibited more fluctuations in %TTR, while those with the VKORC1 GA & CYP2C9*1/*1 genotype (15.1%) tended to exhibit subtherapeutic %TTR. Based on these data, a population K/PD model was developed to capture warfarin treatment response, and a GAI-based approach was used to optimize pharmacogenetics-based dosing regimens for Chinese patients. Our results suggest that for those Chinese patients with the VKORC1 AG/CYP2C9*1/*1 and VKORC1 AA/CYP2C9*1/*3 genotypes, GAI-assisted dosing based on clinical and genetic characteristics offers a means of greatly enhancing the efficacy and safety of warfarin dosing. At present, genetic testing for VKORC1 and CYP2C9 variants may not be covered by health insurance and is not standard practice. There is also a clear need for the development of a convenient smartphone application or similar tool capable of allowing clinicians to input clinical and genetic predictors to facilitate GAI-assisted individualized warfarin dosing recommendations. These two prerequisites will be essential to enable GAI-assisted pharmacogenetic dosing of warfarin as standard practice for anticoagulation management in China. Efforts to educate clinicians and nursing staff regarding the importance of pharmacogenetic dosing strategies will also be needed to ensure the widespread uptake of this approach to individualized patient care.

Abbreviations

A, amount of S-warfarin; AF, atrial fibrillation; AI, artificial intelligence; ALT, alanine transaminase; AST, aspartate aminotransferase; API, Application Programming Interface; BMI, body mass index; BSA, body surface area; CI, confidence interval; CL(S), S-warfarin clearance; COAG, Clarification of Optimal Anticoagulation through Genetics; CPIC, Clinical Pharmacogenetics Implementation Consortium; CSV, Comma-Separated Values; CWRES, conditional weighted residuals; CYP2C9 (*1/*1, *1/*3, *3/*3), Cytochrome P450 family 2 subfamily C member 9, 1075 A>C, *1/*1: wildtype genotype, 1075 A>C, *1/*3: heterozygous genetic variants associated with reduced warfarin metabolism, 1075 A>C, *3/*3: homozygous genetic variants associated with low warfarin metabolism, has the lowest dose requirements; CYP4F2, Cytochrome P450 Family 4 Subfamily F Member 2; DOAC, direct oral anticoagulants; DR, dosing rate; EC₅₀, Effective Concentration 50%; EDK₅₀, dose rate leading to 50% inhibition; EFF, drug effect; E_{max}, maximum drug effect; EU-PACT, European Pharmacogenetics of Anticoagulant Therapy; GAI, generative artificial intelligence; GFR, glomerular filtration rate; GGCX, Gamma-Glutamyl

Carboxylase; GOF, goodness-of-fit; γ , shape factor; HT, height; IIV, interindividual variability; INR, international normalized ratio; INR_{baseline}, baseline INR of each patient; INR_{max}, maximum INR response; IQR, interquartile range; IWPC, International Warfarin Pharmacogenetics Consortium; K/PD, kinetic/pharmacodynamic; LLM, large language model; ML, machine learning; MTT, mean transit time; μ_{INR} , mean maintenance INR; NONMEM, nonlinear mixed effects modeling; PCR, Polymerase Chain Reaction; PD, pharmacodynamic; PK, pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; PRS, Polygenic Risk Scores; Q1, 25th percentile; Q3, 75th percentile; RSE, Relative Standard Error; σ_{INR} , INR fluctuation stability (standard deviation); SD, standard deviation; %TTR, percent time in the therapeutic range; URL, Uniform Resource Locator; V, volume of distribution; VKORC1 (GG/GA/AA), Vitamin K epoxide reductase complex subunit 1, -1639 GG: wildtype genotype, -1639 GA: heterozygous genetic variants that results in a reduction in the required warfarin dose, -1639 AA: homozygous genetic variants that results in increased sensitivity to warfarin, has the lowest dose requirements; VPC, visual predictive check; WT, weight.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

FLL and DYN were responsible for data analysis and writing of the original draft. SKL, YW, YQC, and BL were responsible for study execution. JLP was responsible for data collection. JYY and ZLP were responsible for AI dose optimization. JXD was responsible for project conceptualization and review of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Biomedical Research Ethics Subcommittee of Henan University (Approval No.: HUSOM2022-84). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients enrolled in this study, and patient data were anonymized and de-identified prior to analysis.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors used Qwen2.5-72B-Instruct to interpret clinical inputs to perform simulations and coordinate the AI-assisted warfarin dose optimization workflow. The AI-assisted workflow and its outputs were subject to human oversight and validation. The final dosing recommendations were determined using the K/PD model and deterministic numerical optimization algorithms, rather than being directly generated by the LLM. No identifiable patient data were uploaded to the AI tool, and AI was not used to generate original research data or images or to replace the authors' scientific judgment in interpreting the results and drawing conclusions. The authors take full responsibility for the accuracy, integrity, completeness, and interpretation of the research and its findings.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/Pharmazie58987>.

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