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ARTICLE

Population pharmacokinetic-pharmacodynamic modeling of clopidogrel for dose regimen optimization based on CYP2C19 phenotypes: A proof of concept study

Yun Seob Jung[1] | **Byung Hak Jin**[2] | **Min Soo Park**[2,3] | **Choon Ok Kim**[2] | **Dongwoo Chae**[4]

[1]Department of Convergence Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

[2]Department of Clinical Pharmacology, Severance Hospital, Yonsei University Health System, Seoul, Korea

[3]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea

[4]Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea

Correspondence
Dongwoo Chae, Department of Pharmacology, Yonsei University College of Medicine 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: dongy@yuhs.ac

Choon Ok Kim, Department of Clinical Pharmacology, Severance Hospital, Yonsei University Health System, Seoul, Korea.
Email: delivery98@yuhs.ac

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Abstract

Clopidogrel is an antiplatelet drug used to reduce the risk of acute coronary syndrome and stroke. It is converted by CYP2C19 to its active metabolite; therefore, poor metabolizers (PMs) of CYP2C19 exhibit diminished antiplatelet effects. Herein, we conducted a proof-of-concept study for using population pharmacokinetic-pharmacodynamic (PK-PD) modeling to recommend a personalized clopidogrel dosing regimen for individuals with varying CYP2C19 phenotypes and baseline P2Y12 reaction unit (PRU) levels. Data from a prospective phase I clinical trial involving 36 healthy male participants were used to develop the population PK-PD model predicting the concentrations of clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, and linking clopidogrel H4 concentrations to changes in PRU levels. A two-compartment model effectively described the PKs of both clopidogrel and clopidogrel carboxylic acid, and a one-compartment model of those of clopidogrel H4. The CYP2C19 phenotype was identified as a significant covariate influencing the metabolic conversion of the parent drug to its metabolites. A PD submodel of clopidogrel H4 that stimulated the fractional turnover rate of PRU levels showed the best performance. Monte Carlo simulations suggested that PMs require three to four times higher doses than extensive metabolizers to reach the target PRU level. Individuals within the top 20th percentile of baseline PRU levels were shown to require 2.5–3 times higher doses than those in the bottom 20th percentile. We successfully developed a population PK-PD model for clopidogrel considering the impact of CYP2C19 phenotypes and baseline PRU levels. Further studies are necessary to confirm actual dosing recommendations for clopidogrel.

Choon Ok Kim and Dongwoo Chae contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Among various CYP isoenzymes, CYP2C19 plays a critical role in the conversion of clopidogrel to its active form, clopidogrel H4. Poor metabolizers (PMs) are associated with diminished platelet aggregation when administered a standard dose of 75 mg once daily, and effective methods to optimize the dose in these individuals have not been established. Most authorities recommend prescribing alternative antiplatelet drugs for these patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to determine whether an effective dosing strategy could be devised to optimize the treatment outcome in PMs of clopidogrel using population pharmacokinetic-pharmacodynamic modeling.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provides a proof-of-concept (PoC) of how to derive an individualized clopidogrel dosing regimen that accounts for both the CYP2C19 phenotype and pretreatment P2Y12 reaction unit (PRU) level, two important sources of interindividual variability affecting treatment outcomes.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Our novel dosing guideline can be used as a PoC to instigate future exploratory and validation studies to achieve better therapeutic effects in patients with different CYP2C19 phenotypes and baseline PRU levels and provide an alternative personalization strategy in PMs when switching to other antiplatelet drugs is not an option.

INTRODUCTION

Clopidogrel is an antiplatelet drug that is frequently prescribed to prevent symptoms of atherosclerosis in patients with ischemic stroke, acute coronary syndrome (ACS), and atrial fibrillation.[1–3] In patients with atrial fibrillation, clopidogrel administration has been shown to effectively reduce the risk of thromboembolism.[1]

Clopidogrel is rapidly absorbed after oral administration. Approximately 85% of the oral dose is metabolized by carboxylesterase 1 to form clopidogrel carboxylic acid.[4] The remaining 15% of the oral dose is metabolized by CYP2C19, CYP1A2, and CYP2B6 to form 2-oxo-clopidogrel,[4,5] which is further metabolized to clopidogrel thiol H4 (clopidogrel H4), the active moiety. Among the aforementioned CYP isoenzymes, CYP2C19 plays a predominant role in the conversion of clopidogrel to clopidogrel H4. Consequently, subjects with low CYP2C19 activity exhibit lower clopidogrel H4 concentrations,[6] reduced inhibition of platelet aggregation, and higher rates of thrombotic events than those with normal or high CYP2C19 activity at the same clopidogrel dose.[6–10]

Clopidogrel H4 binds irreversibly to P2Y12 receptors on platelet surfaces,[11] which are chemoreceptors for adenosine diphosphate (ADP) belonging to the G_i class of G protein-coupled purinergic receptors.[12–14] Clopidogrel competes with ADP in binding to P2Y12 receptors and inhibits the activation of the glycoprotein IIb/IIIa complex and ultimately platelet aggregation.[11,14] The degree of P2Y12 receptor inhibition is reported using the P2Y12 reaction unit (PRU),[15] a surrogate end point indicative of the degree of platelet aggregation. The normal baseline PRU values range from 180 to 376.[16] This range must be appropriately managed to prevent adverse effects related to bleeding and thromboembolic events, with excessively low or high values, respectively, linked to an increased risk of bleeding or atherothrombotic and/or thromboembolic events.[15]

The conventional approach to clopidogrel dosing consists of a daily oral administration of a 75 mg dose for individuals identified as CYP2C19 extensive metabolizers (EMs).[3,17] Accompanying this, a loading dose of 300 mg is often prescribed in ACS,[3,18,19] whereas non-ACS patients may receive the same without the loading dose.[3,17,20] Yet, this standardized regimen may falter with CYP2C19 intermediate metabolizers (IMs) and poor metabolizers (PMs). Studies have revealed that in these phenotypes, the standard dose is frequently linked to diminished platelet inhibition and increased instances of therapeutic

failure,[6–10] underscoring an urgent need for refined dosing strategies. Evidence from the ADAPT-DES trial indicates that both excessively high and low PRU levels correlate with suboptimal clinical outcomes.[21] This suggests the existence of a therapeutic window within which platelet inhibition is optimal, necessitating careful dose adjustments. Consequently, patients with higher baseline PRU levels would likely benefit from an increased clopidogrel dosage to align within this therapeutic window. Despite these complexities, current practice lacks individualized dosing protocols tailored to diverse CYP2C19 phenotypes and baseline PRU levels. The only specific guidance offered is the recommendation to prescribe alternative antiplatelet drugs to IMs and PMs,[20] leaving a significant gap in patient-centered care for those requiring clopidogrel therapy.

Although pharmacokinetic (PK) and PK-pharmacodynamic (PK-PD) models for clopidogrel have been developed previously,[5–7,9,10] model-based optimization of the clopidogrel dose considering both the CYP2C19 phenotype and baseline PRU levels has not been sufficiently investigated. Therefore, this study was conducted as a proof-of-concept (PoC) study aimed to develop a population PK-PD model of clopidogrel and platelet aggregation, identify the effects of the CYP2C19 phenotype and interindividual variability (IIV) of baseline PRU levels on clopidogrel PKs and PDs, and propose an individualized dosing regimen based on these factors.

METHODS

Subjects and data

Data were prospectively collected from 36 healthy male participants who participated in a phase I clinical trial. This study was approved by the Institutional Review Board (IRB) of Yonsei University Severance Hospital (IRB approval number: 4-2019-0740), is registered at clinicaltrials.gov (NCT number: NCT04171687), and was conducted at Severance Hospital in Seoul, South Korea, from October 2019 to April 2020.

Eligible subjects were healthy male adults aged 19–55 years, with body weights ranging from 55 to 90 kg, and body mass index between 18.5 and 27.0 kg/m^2. Subjects with clinically significant diseases affecting the pulmonary, cardiovascular, hepatobiliary, neurological, endocrine, or immune systems were excluded. Additionally, exclusion criteria included current smokers, individuals with gastrointestinal diseases or surgeries affecting drug absorption, those with a clinically significant bleeding history, and those whose PRU values at screening fell outside ±10% of the upper/lower limit of the normal range.

Upon admission, blood samples were collected to determine the CYP2C19 phenotype. One day later, the subjects received a 75 mg tablet of clopidogrel orally once daily for 7 days to attain maximum platelet inhibition.[22] Loading dose was not given, aligning with common practices outside acute coronary syndrome scenarios.[3,17,20] Blood samples were collected at predose, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h. After the last blood sample collection, all the subjects were discharged from the hospital.

The concentrations of clopidogrel and clopidogrel carboxylic acid were measured at all sampling times, whereas the concentrations of clopidogrel H4 were measured predose, 0.33, 0.67, 1, 2, 4, and 6 h after dosing. PRU values were determined at predose on days 1, 3, 5, and 7, and 1, 4, 6, and 24 h after dosing on day 7. The PRU value was measured twice at each sampling time, and the arithmetic mean value was used as the end point.

The following demographic and laboratory data were collected: age, body weight, height, blood urea nitrogen, serum creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, γ-glutamyl transferase, and CYP2C19 phenotype.

Plasma assay for PK, PD, and CYP phenotyping

For PK analysis, blood samples (~6 mL) were collected in tubes containing EDTA-K2 and centrifuged (3000 rpm, 4°C, 10 min) for 30 min. The supernatant was then preserved at −70°C or lower, and the temperature during transportation to the analysis institute was maintained at a level that did not affect the stability of the samples. Clopidogrel and its metabolite concentrations were analyzed by liquid chromatography-mass spectrometry after plasma separation from each blood sample.[23,24] The calibration ranges and correlation coefficients (γ) were 0.09–10 ng/mL with γ greater than or equal to 0.9985, 0.3–50 ng/mL with γ greater than or equal to 0.9987, and 50–5000 ng/mL with γ greater than or equal to 0.9987 for clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, respectively. The lower limits of quantification (LLOQs) for the assays were 0.09, 0.3, and 50 ng/mL for clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, respectively. Following the intra- and inter-day assays, the accuracies were found to be within the range of 85%–115% (LLOQ: 80%–120%), and all precisions were less than 15% (LLOQ: <20%) in the coefficient of variation (CV).

For the PD analysis, blood samples of ~4 mL were collected into dedicated citrate tubes. During collection, turbulence and hemolysis were prevented, and the collected blood was mixed with an anticoagulant by inverting the

tube. Blood samples for PD analysis were stored at 25°C (room temperature) and analyzed within 4 h of collection. PRU was measured in whole blood using the VerifyNow system and VerifyNow P2Y12 assay kit (Accumetrics).[15,22]

Genetic analysis to determine the CYP2C19 phenotype was conducted for all participants on the day they were admitted to Severance Hospital. Approximately 2 mL of blood was collected in tubes containing EDTA-K2 and analyzed. The subjects were classified as EM, IM, or PM based on their CYP2C19 genotype.

Population PK-PD analysis

Analysis was performed using MonolixSuite 2021R2, with the stochastic approximation expectation maximization algorithm used for parameter estimation.[25] Data exploration and a graphical representation of the results were conducted using R version 4.2.2. For the samples below quantification limit (BQL), the M4 method was utilized. This approach is based on the simultaneous modeling of BQL observations and observations above the LLOQ, treating BQL observations as categorical data and constraining them to values greater than zero and less than the LLOQ.[26]

A sequential PK-PD modeling process was implemented.[27] First, a PK model was developed for clopidogrel and its metabolites. Subsequently, all PK parameters obtained from the final PK model were fixed, and the PD parameters were estimated by linking the PK model to the PD model.

PK model

A model was developed to jointly predict the PKs of the parent drug and its metabolites. To account for first-pass metabolism, a hepatic compartment was inserted between the depot and central compartments.[6] In the hepatic compartment, we assumed that the parent drug was converted into one of the following metabolites: clopidogrel H4, clopidogrel carboxylic acid, or others. We further assumed that all parent drugs ultimately underwent metabolism in the hepatic compartment.

Given the molecular weights of clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, viz. 321.82, 355.83, and 307.80 g/mol, respectively, we applied scaling factors of 1.106 and 0.956 to the formation rates of clopidogrel H4 and clopidogrel carboxylic acid, respectively.[28–30] The fractions of the dose metabolized to clopidogrel H4 (fm_{H4}), clopidogrel carboxylic acid (fm_{carbo}), and others (fm_{others}) were set to $fm_1 \bullet fm_2$, $(1 - fm_1) \bullet fm_2$ and $1 - fm_2$, respectively, with 0 less than or equal to fm_1, fm_2 less than or equal to 1. Because of parameter unidentifiability, we set the hepatic volume to be the same as the central volume and fixed the typical fm_1 and fm_2 values to 0.125 and 0.96, respectively, based on the known fractions metabolized to clopidogrel H4 and clopidogrel carboxylic acid, which were ~10–15% and 85%, respectively.[4,5]

PK-PD model

In accordance with the sequential PK-PD modeling framework, we fixed all PK parameters to the estimates obtained from the final PK model. The PRU level was used as the PD end point, and its changes were linked to the concentration of clopidogrel H4. A turnover model in which clopidogrel H4 stimulated the decline in PRU levels was identified as the best PD model.[31] The structure of the PK-PD model is depicted in Figure 1.

IIV associated with the model parameters was modeled as:

$$P_i = \text{TVP} \bullet \exp(\eta_i).$$

$$\text{or } \log\left(\frac{P_i}{1 - P_i}\right) = \log\left(\frac{\text{TVP}}{1 - \text{TVP}}\right) + \eta_i \text{ for } fm_1 \text{ and } fm_2$$

where TVP is the typical value of the parameter (P), P_i is the parameter for the ith individual, and η_i is a random effect representing the inter-individual difference, which is assumed to be normally distributed with a mean of zero and variance of ω^2. For fm_1 and fm_2, whose values were constrained between 0 and 1, IIVs were applied using a logit function. We estimated the correlation coefficients between parameters when they were deemed physiologically plausible.

The residual variability was modeled as:

$$Y_{ij} = F_{ij} \bullet (1 + \varepsilon_{\text{Pro},ij}) + \varepsilon_{\text{Add},ij}$$

where Y_{ij} and F_{ij} are the jth measured observation and model prediction of the ith individual, respectively, and $\varepsilon_{\text{Pro},ij}$ and $\varepsilon_{\text{Add},ij}$ are proportional and additive residual errors, which are normally distributed with a mean of zero and variances of ${\sigma_{\text{Prop}}}^2$ and ${\sigma_{\text{Add}}}^2$, respectively.

Covariate model

We explored parameter-covariate relationships based on correlation tests between patient covariates and the individual η_i. Considering both the physiology and the statistical significance level of the parameter-covariate correlation,

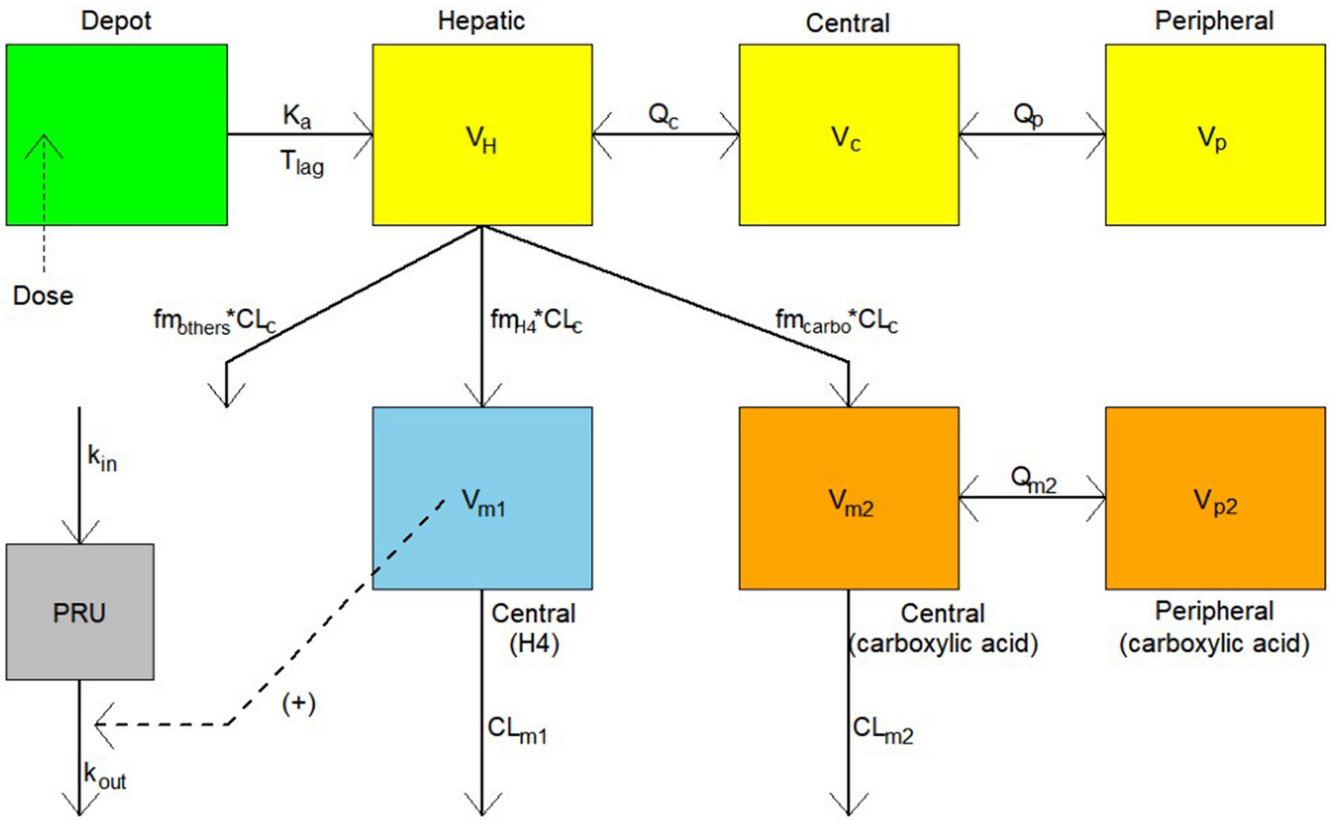

FIGURE 1 A schematic diagram illustrating the structure of the final PK-PD model. The parent drug in the depot is absorbed into the hepatic compartment, which is either metabolized into H4, carboxylic acid, and others or distributed to the central (plasma) and peripheral compartments. The active metabolite, H4, stimulates the elimination of PRU. CL, clearance; PD, pharmacodynamic; PK, pharmacokinetic; PRU, P2Y12 reaction unit.

stepwise covariate modeling was performed with significance levels of p less than 0.01 (objective function value difference [ΔOFV] = 6.63, df = 1) for forward addition and p less than 0.001 (ΔOFV = 10.83, df = 1) for backward deletion, where OFV denotes objective function value.[32] We applied power or exponential functions to continuous covariates and exponential functions for categorical covariates.

(Power function)

$$\mathrm{TVP} = \mathrm{TVP}_0 \bullet \left(\mathrm{COV}/\mathrm{COV}_{\mathrm{med}}\right)^{\beta}$$

(Exponential function)

$$\mathrm{TVP} = \mathrm{TVP}_0 \bullet \exp(\beta \bullet \mathrm{COV})$$

$$\text{or } \mathrm{TVP} = \mathrm{TVP}_0 \bullet \exp\left[\beta \bullet \left(\mathrm{COV} - \mathrm{COV}_{\mathrm{med}}\right)\right]$$

where TVP and TVP_0 denote the typical values of the parameter with and without covariate incorporation, β the regression coefficient, COV the covariate, and $\mathrm{COV}_{\mathrm{med}}$ the median value of the covariate.

The final PK-PD model was evaluated using visual predictive checks (VPCs). At this stage, the precision of the estimated model parameters and plausibility of the parameter-covariate relationships were assessed.

Dose optimization

Based on the final PK-PD model, we simulated the average PRU value at steady-state ($\mathrm{PRU}_{\mathrm{ave,ss}}$) after clopidogrel administration using Simulx 2021R2. Subgroups were defined based on the baseline PRU levels and CYP2C19 phenotypes (EMs, IMs, and PMs). Baseline PRU levels were categorized into five intervals: 180–209, 209–242, 242–280, 280–324, and 324–376 based on the known normal range of 180–376.[16] For each subgroup, we calculated $\mathrm{PRU}_{\mathrm{ave,ss}}$ and the proportion of subjects whose $\mathrm{PRU}_{\mathrm{ave,ss}}$ was within the target range of 70–150.[33,34] We randomly allocated virtual subjects into 15 subgroups (with 1000 virtual subjects in each subgroup), set the dosing scheme to once daily for 3 weeks, and escalated the doses at multiples of 15 mg. The goal of dose optimization was to maximize the proportion of subjects with PRU levels within the target range.

RESULTS

Subjects and data

The baseline demographic and laboratory data of each participant are shown in Table 1. All 36 participants completed the full schedule of the clinical trial. The total numbers of observations for clopidogrel, clopidogrel H4, clopidogrel carboxylic acid, and PRU were 503, 239, 504, and 280, respectively. The proportions of observations BQL were 27.0%, 11.7%, and 3.8% for clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, respectively. No BQLs were observed in the PRU measurements. The PK and PD observations stratified by the CYP2C19 phenotype are shown in Figure S1.

When determining the CYP2C19 phenotype, the *1/*1 and *1/*17 genotypes were classified as EM, *1/*2, *1/*3, *2/*17, and *3/*17 as IM, and *2/*2, *2/*3, and *3/*3 as PM. The numbers of EM, IM, and PM subjects were 17, 15, and four, respectively.

PK-PD modeling

The PK data were effectively described by a two-compartment model for both clopidogrel and clopidogrel carboxylic acid and a one-compartment model for clopidogrel H4. A PK-PD model for clopidogrel H4 stimulating the fractional turnover of PRU showed the best performance. Figure 1 schematically illustrates the overall structure of the final PK-PD model. Table 2 presents parameter estimates for the final model. All parameters were estimated with reasonable precision and had relative standard errors less than 30%. The following system of ordinary differential equations describes the model. For the description of the model variables, refer to the footnotes in Table 2.

$$\frac{dA_a}{dt} = -k_a \bullet A_a, A_a(0) = \text{Dose}$$

$$\frac{dA_H}{dt} = k_a \bullet A_a - \frac{CL_c + Q_c}{V_H} \bullet A_H + \frac{Q_C}{V_c} \bullet A_c$$

$$\frac{dA_c}{dt} = \frac{Q_c}{V_H} \bullet A_H - \frac{Q_C + Q_p}{V_c} \bullet A_c + \frac{Q_p}{V_p} \bullet A_p$$

$$\frac{dA_p}{dt} = \frac{Q_p}{V_c} \bullet A_c - \frac{Q_p}{V_p} \bullet A_p$$

$$\frac{dA_{m1}}{dt} = 1.106 \bullet fm_1 \bullet fm_2 \bullet \frac{CL_c}{V_H} \bullet A_H - \frac{CL_{m1}}{V_{m1}} \bullet A_{m1}, \quad C_{m1} = \frac{A_{m1}}{V_{m1}}$$

$$\frac{dA_{m2}}{dt} = 0.956 \bullet (1 - fm_1) \bullet fm_2 \bullet \frac{CL_c}{V_H} \bullet A_H - \frac{CL_{m2} + Q_{m2}}{V_{m2}} \bullet A_{m2} + \frac{Q_{m2}}{V_{p2}} \bullet A_{p2}$$

$$\frac{dA_{p2}}{dt} = \frac{Q_{m2}}{V_{m2}} \bullet A_{m2} - \frac{Q_{m2}}{V_{p2}} \bullet A_{p2}$$

TABLE 1 Baseline characteristics of the subjects ($N = 36$).

	CYP2C19 phenotype		
Variables	**EM ($n = 17$)**	**IM ($n = 15$)**	**PM ($n = 4$)**
Baseline PRU	207.41 ± 23.60	199.83 ± 28.60	207.50 ± 33.48
Age, year	32.35 ± 6.99	31.27 ± 4.51	27.00 ± 4.90
Weight, kg	71.32 ± 8.04	72.80 ± 8.69	74.93 ± 7.68
Height, cm	172.96 ± 3.89	175.31 ± 5.19	179.00 ± 8.21
AST, IU/L	18.53 ± 4.90	17.93 ± 3.08	17.50 ± 6.95
ALT, IU/L	20.29 ± 12.62	15.40 ± 5.64	15.00 ± 7.75
ALP, IU/L	69.06 ± 14.74	64.40 ± 12.88	72.00 ± 8.87
γ-GT, IU/L	23.12 ± 13.79	22.20 ± 12.19	22.50 ± 10.97
Total bilirubin, mg/dL	0.69 ± 0.11	0.85 ± 0.38	0.80 ± 0.50
Blood urea nitrogen, mg/dL	13.11 ± 3.60	12.87 ± 3.83	12.68 ± 3.17
Serum creatinine, mg/dL	0.91 ± 0.14	0.92 ± 0.15	0.95 ± 0.07
Total protein, g/dL	7.02 ± 0.35	7.19 ± 0.41	6.98 ± 0.30
Albumin, g/dL	4.62 ± 0.21	4.73 ± 0.32	4.58 ± 0.35

Note: All data are shown mean ± standard deviation.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; PRU, P2Y12 reaction unit; γ-GT, gamma-glutamyl transferase.

TABLE 2 Parameter estimates of the final PK-PD model.

Parameters	Population mean	Standard deviation
Clopidogrel		
V_c (=V_H) (L)	1463.92 (7.56)	0.331 (17.7)
V_p (L)	2823.98 (7.72)	
CL_c (L/h)	9257.28 (6.92)	0.343 (17.7)
Cor(V_c, CL_c)		0.702 (21.2)
Q_c (L/h)	845.70 (7.04)	0.307 (17.3)
Q_p (L/h)	587.93 (9.23)	
k_a (h^{-1})	19.64 (28.0)	
T_{lag} (h)	0.196 (4.59)	
$\sigma_{clopidogrel}$	0.357 (2.68)	
Clopidogrel H4 and clopidogrel carboxylic acid		
fm_1	0.125 FIX	0.255 (16.0)
fm_1~IM	−0.450 (29.8)	
fm_1~PM	−0.996 (17.6)	
fm_2	0.960 FIX	1.130 (16.7)
fm_2~IM	−1.428 (29.8)	
fm_2~PM	−2.432 (24.2)	
V_{m1} (L)	51.45 (9.81)	
CL_{m1} (L/h)	74.25 (8.87)	
V_{m2} (L)	17.34 (3.54)	
V_{p2} (L)	51.89 (6.48)	0.285 (17.1)
CL_{m2} (L/h)	7.248 (3.53)	0.123 (14.3)
Q_{m2} (L/h)	4.476 (3.59)	
σ_{H4}	0.363 (3.91)	
σ_{carbo}	0.209 (2.11)	
PRU		
K_{in}	1.225 (3.81)	0.120 (12.7)
K_{out} (h^{-1})	0.006 (3.3)	
E_{max}	57.84 (12.7)	0.501 (15.0)
EC_{50} (ng/mL)	67.32 (12.0)	
Hill	1.851 (7.46)	
σ_{PRU}	13.69 (2.66)	

Abbreviations: CL_c, clearance; CL_{m1}, clearance in clopidogrel H4; CL_{m2}, clearance in clopidogrel carboxylic acid; EC_{50}, concentration which half of maximum response reaches at; fm_1, relative fraction of dose metabolized to clopidogrel H4 within two metabolites; fm_2, fraction of dose metabolized to clopidogrel H4 and clopidogrel carboxylic acid; E_{max}, maximum effect of drug on response; Hill, coefficient of exponent in a sigmoid E_{max} model; IM, immediate metabolizer; k_a, first-order absorption rate constant; K_{in}, turnover rate; K_{out}, fractional turnover rate; PD, pharmacodynamic; PK, pharmacokinetic; PM, poor metabolizer; PRU, P2Y12 reaction unit; Q_c, intercompartmental clearance between hepatic and central compartment; Q_p, intercompartmental clearance between central and peripheral compartment; Q_{m2}, intercompartmental clearance between central and peripheral compartment in clopidogrel carboxylic acid; T_{lag}, lag time of absorption; V_c, volume of central compartment;V_H, volume of hepatic compartment; V_{m1}, volume of central compartment in clopidogrel H4; V_{m2}, volume of central compartment in clopidogrel carboxylic acid; V_p, volume of peripheral compartment; V_{p2}, volume of peripheral compartment in clopidogrel carboxylic acid; σ_{carbo}, proportional error about clopidogrel carboxylic acid; $\sigma_{clopidogrel}$, proportional error about clopidogrel; σ_{PRU}, additive error about PRU; σ_{H4}, Proportional error about clopidogrel H4.

$$\frac{dPRU}{dt} = K_{in} - K_{out} \bullet \left(1 + \frac{E_{max} \bullet C_{m1}^{Hill}}{EC_{50}^{Hill} + C_{m1}^{Hill}}\right) \bullet PRU, \quad PRU(0) = \frac{K_{in}}{K_{out}}$$

$$fm_{H4} = fm_1 \bullet fm_2, \quad fm_{carbo} = (1 - fm_1) \bullet fm_2, \quad fm_{others} = 1 - fm_2$$

PK submodel

IIV was incorporated into V_c(=V_H), CL_c, Q_c, fm_1, fm_2, V_{p2}, and CL_{m2}. For parameter definitions, refer to the footnote of Table 2. CL_c and V_c exhibited a significant positive correlation (Pearson's r=0.702). K_a was estimated to be 19.64 h^{-1}, corresponding to an absorption half-life of 2.13 min. We assumed a logit-normal distribution for fm_1 and fm_2 and calculated the CV% of IIV using the Delta method.[35] The CV% of fm_1 and fm_2 were 24.52% and 2.78% in EMs, 26.44% and 11.13% in IMs, and 27.78% and 27.87% in PMs, respectively. The only significant covariate was the CYP2C19 phenotype in fm_1 and fm_2. A proportional residual error model was selected for all end points, with estimated magnitudes of 35.7%, 36.3%, and 20.9% for clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, respectively.

The VPCs of the final PK model are shown in Figure 2a–c. The model predictions were concordant with the observations; 93.44%, 95.82%, and 96.03% of the total observations were within 90% of the prediction intervals (5th–95th percentiles) for clopidogrel, clopidogrel H4, and clopidogrel carboxylic acid, respectively.

PD submodel

The typical baseline PRU level was estimated as 212.67 (calculated as K_{in}/K_{out}). IIV was incorporated into K_{in} and E_{max}. K_{out} was estimated to be 0.00576 h^{-1} (≈0.006), corresponding to a half-life of 5 days. E_{max} was estimated to be 57.84, implying a maximum reduction in PRU at a steady state of 1.7% ($\frac{1}{1+57.84}$). The standard deviation (ω) associated with the IIV of E_{max} was estimated to be 0.501, suggesting substantial variability in drug efficacy among subjects with the same CYP2C19 phenotype. No significant covariates were found to affect the PDs of clopidogrel. The additive residual error model yielded an estimated error magnitude of 13.69.

The VPC of the final PD model is shown in Figure 2d. The model predictions showed good fit with the observations. Of the total observations, 90.71% were within 90% prediction intervals (5th–95th percentiles).

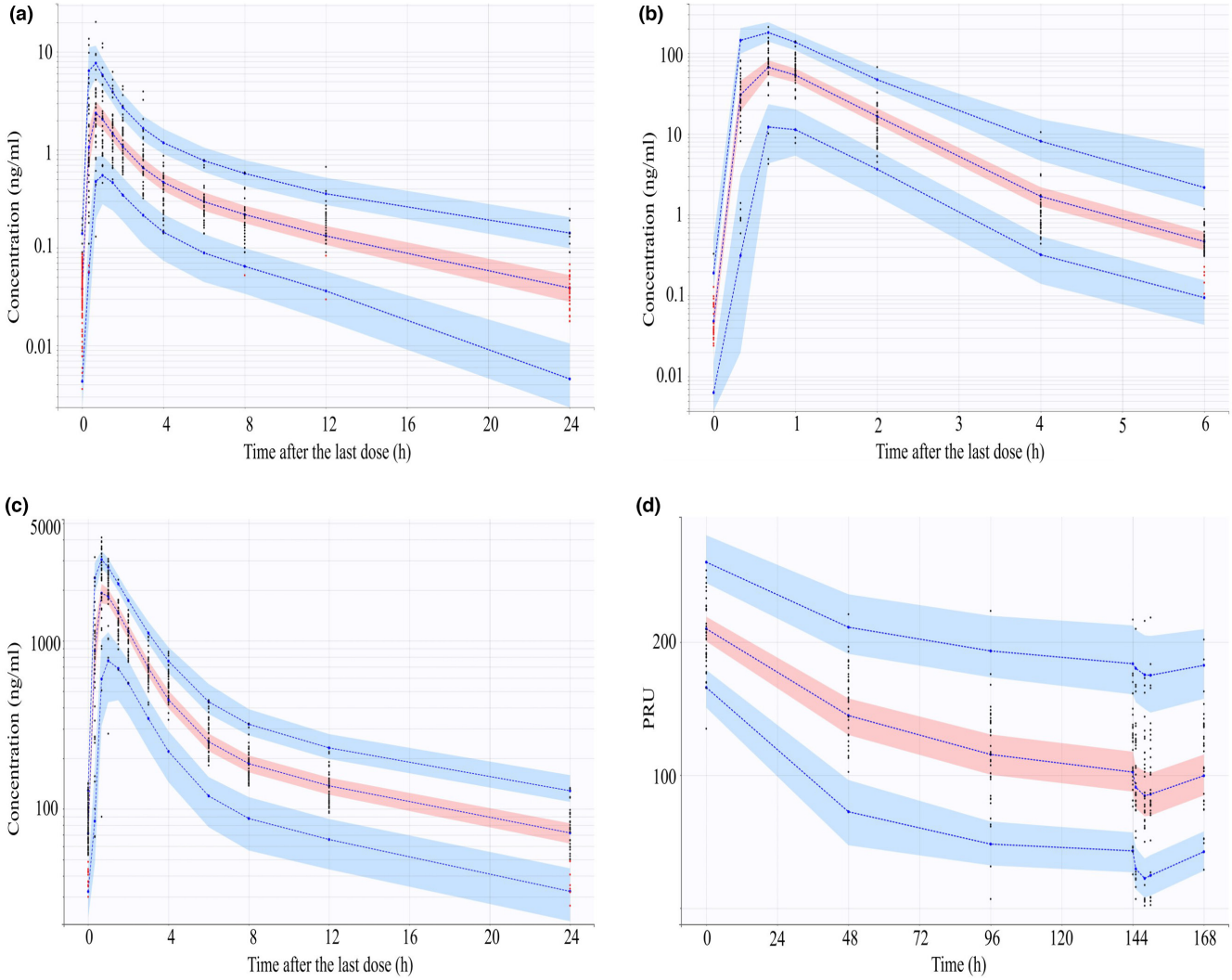

FIGURE 2 Visual predictive checks of the final PK-PD model. Black and red dots represent observations above and below LLOQ, respectively. Blue dashed lines represent 5th, median, and 95th percentiles of predictions and each shaded area represents the corresponding 90% confidence interval. (a) Clopidogrel; (b) clopidogrel H4; (c) clopidogrel carboxylic acid; (d) PRU. LLOQ, lower limit of quantification; PD, pharmacodynamic; PK, pharmacokinetic; PRU, P2Y12 reaction unit.

Impact of CYP2C19 phenotype on clopidogrel PKs

Covariate model building showed that fm_1 and fm_2 were significantly different among CYP2C19 phenotypes. We calculated the fractions metabolized to clopidogrel H4 (fm_{H4}) and clopidogrel carboxylic acid (fm_{carbo}) using fm_1 and fm_2 estimates. Table 3 summarizes the estimated fractions that were converted into different metabolites. The predicted fm_{H4}/fm_{carbo} values for EMs, IMs, and PMs were 0.120/0.84, 0.071/0.781, and 0.034/0.644, respectively. Specifically, fm_{H4} and fm_{carbo} in IMs decreased to 59.2% and 93.0% of those in the EMs, respectively. Regarding PMs, fm_{H4} and fm_{carbo} decreased to 28.3% and 76.7% of those in the EMs, respectively. Although CYP2C19 affected the rate of conversion of both metabolites, fm_{H4} was more sensitive compared to fm_{carbo}. Conversely, fm_{others} increased to 0.148 and 0.322 for IMs and PMs, respectively, compared with 0.040 for EMs.

TABLE 3 Fraction of dose metabolized to clopidogrel H4, clopidogrel carboxylic acid, and others stratified by CYP2C19 phenotype.

	fm_1	fm_2	fm_{H4}	fm_{carbo}	fm_{others}
EM	0.125	0.960	0.120	0.840	0.040
IM	0.083	0.852	0.071	0.781	0.148
PM	0.050	0.678	0.034	0.644	0.322

Abbreviations: EM, extensive metabolizer; fm_{carbo}, fraction of dose metabolized to clopidogrel carboxylic acid $=(1 - fm_1) \bullet fm_2$; fm_{H4}, fraction of dose metabolized to clopidogrel H4 $= fm_1 \bullet fm_2$; fm_{others}, fraction of dose metabolized to other metabolites $= 1 - fm_2$; IM, intermediate metabolizer; PM, poor metabolizer.

Simulations for optimal dosing regimen stratified by CYP2C19 phenotype and baseline PRU level

We performed Monte Carlo simulations of the final PK-PD model using different doses by random sampling from the estimated parameter-covariance matrix and calculated steady-state PRU levels ($PRU_{ave,ss}$) to guide dose optimization. Table 4 summarizes the optimal doses for achieving the target therapeutic range of $PRU_{ave,ss}$. The $PRU_{ave,ss}$ and the proportion of subjects whose $PRU_{ave,ss}$ was within the target range after being given the optimal dose, stratified by baseline PRU level and CYP2C19 phenotype, are described in the Table S1. $PRU_{ave,ss}$ distributions of the different strata are shown in Figure 3.

The optimal doses differed among baseline PRU levels and CYP2C19 phenotypes. The predicted optimal maintenance doses for once-daily administration ranged between 30 and 90, 60 and 150, and 120 and 300 mg for EMs, IMs, and PMs, respectively. Simulation results suggested that IMs and PMs require 1.5–2 times and 3–4 times higher doses than EMs to achieve the target PRU level, respectively. Furthermore, subjects in the top 20th percentile (324–376) of baseline PRU levels were shown to require 2.5–3 times higher doses than those in the lowest 20th percentile (180–209). In patients with ACS, the optimal loading dose was calculated by multiplying the proposed dose by four.

TABLE 4 Optimal doses stratified by baseline PRU level and CYP2C19 phenotype.

	Optimal dose		
	EM	IM	PM
180–208.99	30 mg q.d.	60 mg q.d.	120 mg q.d.
209–241.99	45 mg q.d.	75 mg q.d.	150 mg q.d.
242–279.99	60 mg q.d.	90 mg q.d.	180 mg q.d.
280–323.99	75 mg q.d.	120 mg q.d.	240 mg q.d.
324–375.99	90 mg q.d.	150 mg q.d.	300 mg q.d.

Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; PRU, P2Y12 reaction unit.

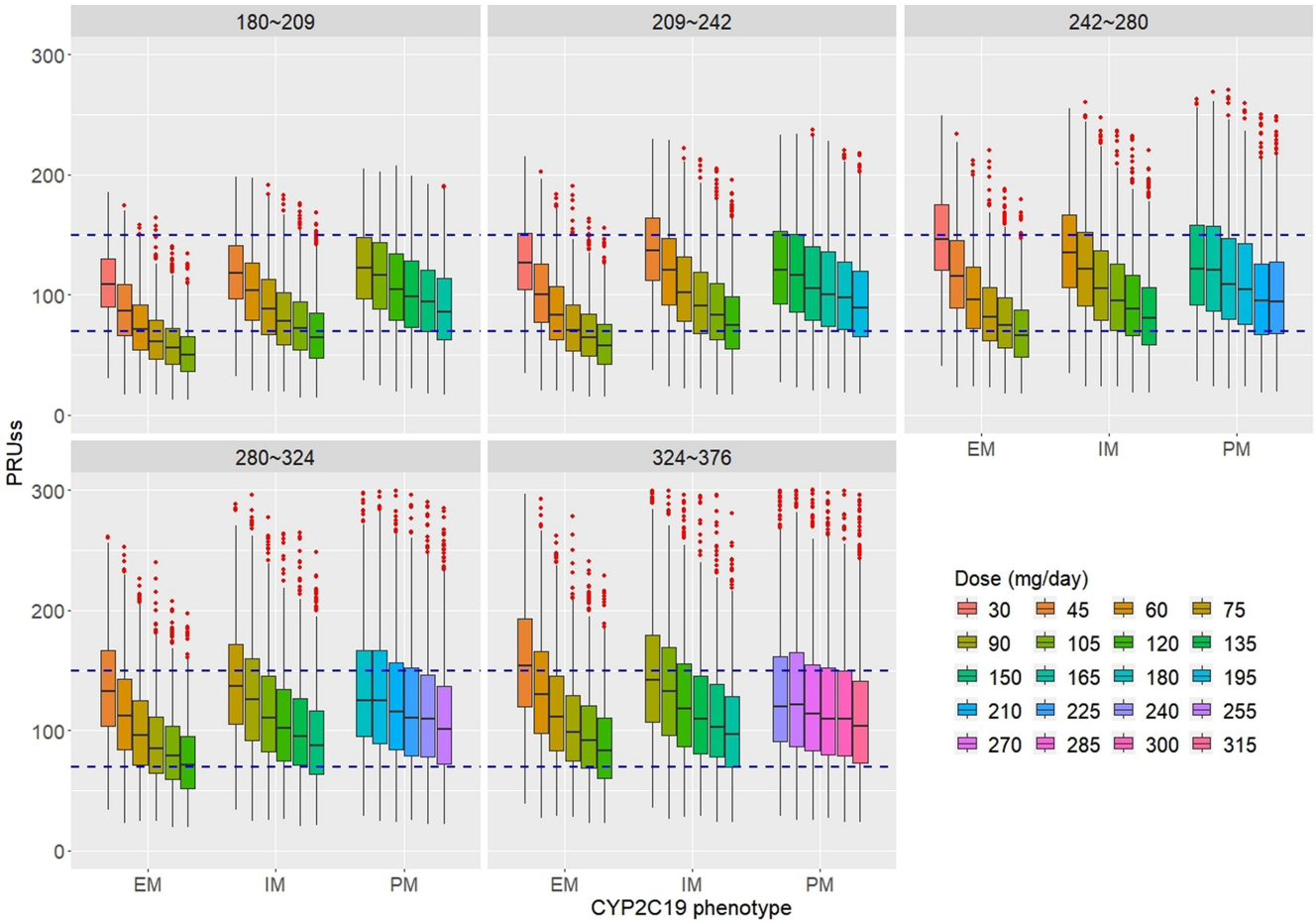

FIGURE 3 Distributions of $PRU_{ave,ss}$ given different doses stratified by baseline PRU levels and CYP2C19 phenotypes. The colored bars and red dots represent the predicted interquartile ranges and outliers of $PRU_{ave,ss}$, respectively. The two blue dashed lines represent the lower (=70) and upper (=150) bounds of $PRU_{ave,ss}$ therapeutic range. PRU_{ss}, P2Y12 reaction unit at steady-state.

The simulated median $PRU_{ave,ss}$ was within the range of 95–110. There was large IIV in $PRU_{ave,ss}$ among virtual subjects in each subgroup, decreasing in the order of PMs, IMs, and EMs owing to the positive dependence of IIV magnitude on baseline PRU levels. The results additionally showed that $PRU_{ave,ss}$ ratios of the 95th percentile to 5th percentile in IMs and PMs were 1.01–1.22 times and 1.15–1.30 times higher than those in EMs, respectively. The ratios in the highest 20th percentile of the baseline PRU levels were 1.28–1.54 times higher than those in the lowest 20th percentile. In contrast, the proportion of subjects within the target PRU range decreased in the order of EMs, IMs, and PMs, which were 63.9–80.8%, 62.8–73.1%, and 57.6–69.7%, respectively, owing to their dependence on the baseline PRU level. Given the same CYP2C19 phenotype, the proportions in the highest 20th percentile of baseline PRU levels were ~12%–17% lower than those in the lowest 20th percentile.

DISCUSSION

The 2022 US Food and Drug Administration-approved drug label for clopidogrel includes a boxed warning regarding diminished antiplatelet effects in CYP2C19 PM. This warning advocates for the use of another platelet P2Y12 inhibitor or alternative dosing strategies in these individuals.[36]

In a prospective randomized crossover trial, Collet et al. assessed the PK-PD responses to a standard (300 mg) versus high (900 mg) loading dose of clopidogrel according to the carrier status of the CYP2C19 allele.[37] The results demonstrated that the use of a high loading dose could overcome genetic resistance among heterozygous, but not homozygous carriers of loss-of-function (LOF) allele. Aleil et al. reported that maintenance therapy with a high dose of 150 mg/day enhanced the treatment response in the majority of low responders.[38] However, studies using higher maintenance doses of clopidogrel have shown disappointing results in carriers of the homozygous CYP2C19 LOF allele.[39] Overall, there is inconclusive evidence to support the use of higher doses of clopidogrel in PMs.

Nevertheless, dual antiplatelet therapy with clopidogrel and aspirin remains the standard of care for preventing recurrent ischemic events in patients undergoing percutaneous coronary intervention.[40] Clopidogrel is also reportedly associated with a lower bleeding risk than the more recently introduced platelet inhibitors and is less expensive.[41] Hence, personalized clopidogrel dosing regimens for PMs are needed.

The ADAPT-DES, a large multicenter observational study involving 8583 patients, demonstrated the importance of achieving an ideal level of PRU for optimal clinical outcome.[21] Increased PRU levels were associated with a monotonic increase in stent thrombosis, whereas bleeding risk was confined to the lowest PRU quintile, suggesting an optimal therapeutic window for platelet inhibition. Given the large IIV associated with pretreatment PRU levels, it is likely that better strategies to personalize clopidogrel doses would consider both the CYP2C19 phenotype and baseline PRU level.

Herein, we developed a PK-PD model for clopidogrel to provide a framework for an optimal dosing regimen tailored to different CYP2C19 phenotypes and baseline PRU levels. Our results suggest that the optimal maintenance dose of clopidogrel in PMs with a typical pretreatment PRU level within the range of 242–280 is 180 mg. Individuals with higher pretreatment PRU levels in the range of 324–376 require a maintenance dose as high as 300 mg to achieve a therapeutic PRU window of 70–150.[33,34] The probability of attaining a therapeutic PRU level under the proposed optimal doses decreased with higher pretreatment PRU levels. In PMs, individuals with pretreatment PRU in the lowest quintile of 180–209 attained therapeutic PRU levels of ~70%, but only 58% was attained in the highest quintile of 324–376. These results offer potential explanations for the failures reported in previous studies.[8,37] First, the maintenance dose used in these previous reports, although higher than the standard dose, may have been insufficient to achieve a therapeutic effect. Second, the highly variable pretreatment PRU levels might have resulted in a lower statistical power to detect a significant clinical benefit.

The implications of our study are as follows: On one hand, it opens new avenues to better adapt clopidogrel dosing according to different CYP2C19 phenotypes and pretreatment PRU levels. In contrast, the expected treatment success rate under the optimal dosing regimen was modest; the maximum expected success probability was merely around 70% (Table S1), which was attained in individuals with low pretreatment PRU levels. Given these aspects, conclusions from previous studies that claim no significant benefit from an increased clopidogrel dose are understandable.[20]

To assess the face validity of our model, we compared the model parameter estimates with those reported in previously developed population PK-PD models.[5–7] Overall, the clearance-related parameter values were similar; however, the volume-related parameter values displayed some differences. Potential causes are differences in sampling time, race, or model structure.

The core novelty of our proposed dosing regimen is the consideration of pretreatment PRU levels, in addition to CYP2C19 phenotype. This resulted in a substantial reduction in the variability of treatment outcomes.

Because the baseline PRU level can easily be measured before the initiation of clopidogrel therapy, its consideration in optimizing the clopidogrel dose constitutes a feasible strategy. Precise documentation of the baseline PRU value also enables a more accurate assessment of the degree of inhibition of platelet aggregation ($\text{IPA} = 1 - \frac{\text{Target PRU}}{\text{Baseline PRU}}$).

This study has some limitations. First, we did not distinguish between CYP2C19 ultra metabolizers (UMs) and EMs. Although some subjects harbored the *1/*17 genotype, we classified both *1/*1 and *1/*17 as EM. If we had included subjects with the *17/*17 genotype, we could have explored the effect of CYP2C19 UM on the PKs and PDs of clopidogrel and developed a more detailed dosing regimen. Second, we optimized the dose based on the CYP2C19 phenotype rather than genotype. Different genotypes may have different CYP2C19 activities even if they belong to the same phenotype. However, given the small number of subjects, dose optimization stratified by genotype was difficult. Third, all subjects were healthy adult men, rendering the identification of additional covariates affecting the PK-PD of clopidogrel nearly impossible. There were no women and patients with cardiovascular diseases. Fourth, the sample size was small with only 36 subjects. Fifth, there is no universally accepted target range for PRU. Therefore, the optimal clopidogrel dose can change if alternative target ranges are used. Finally, our model was not externally validated with a larger population including women or patients. Therefore, our study should be considered as a PoC study with all its conclusions requiring further external validation. Owing to this, prospective clinical trials are required to validate our results and to gain firm confidence regarding our dosing scheme.

In conclusion, we successfully developed a population PK-PD model for clopidogrel by considering the impact of varying CYP2C19 phenotypes and baseline PRU levels. We suggest that clopidogrel dosing should consider both an individual's CYP2C19 phenotype and baseline PRU level.

AUTHOR CONTRIBUTIONS

Y.S.J., B.H.J., D.C., and C.O.K. wrote the manuscript. B.H.J., M.S.P., D.C., and C.O.K. designed the research. Y.S.J., B.H.J., M.S.P., D.C., and C.O.K. performed the research. Y.S.J. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

ORCID

Yun Seob Jung https://orcid.org/0000-0002-5760-4054
Choon Ok Kim https://orcid.org/0000-0002-2319-1108
Dongwoo Chae https://orcid.org/0000-0002-7675-3821

REFERENCES

1. Maegdefessel L, Azuma J, Tsao PS. Modern role for clopidogrel in management of atrial fibrillation and stroke reduction. *Vasc Health Risk Manag*. 2010;6:95-103.
2. Patti G, Micieli G, Cimminiello C, Bolognese L. The role of clopidogrel in 2020: a reappraisal. *Cardiovasc Ther*. 2020;2020:8703627.
3. Zambahari R, Kwok OH, Javier S, et al. Clinical use of clopidogrel in acute coronary syndrome. *Int J Clin Pract*. 2007;61:473-481.
4. Sangkuhl K, Klein TE, Altman RB. Clopidogrel pathway. *Pharmacogenet Genomics*. 2010;20:463-465.
5. Duong JK, Nand RA, Patel A, Della Pasqua O, Gross AS. A physiologically based pharmacokinetic model of clopidogrel in populations of European and Japanese ancestry: An evaluation of CYP2C19 activity. *Pharmacol Res Perspect*. 2022;10:e00946.
6. Jiang XL, Samant S, Lewis JP, et al. Development of a physiology-directed population pharmacokinetic and pharmacodynamic model for characterizing the impact of genetic and demographic factors on clopidogrel response in healthy adults. *Eur J Pharm Sci*. 2016;82:64-78.
7. Danielak D, Karazniewicz-Lada M, Komosa A, et al. Influence of genetic co-factors on the population pharmacokinetic model for clopidogrel and its active thiol metabolite. *Eur J Clin Pharmacol*. 2017;73:1623-1632.
8. Simon T, Bhatt DL, Bergougnan L, et al. Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. *Clin Pharmacol Ther*. 2011;90:287-295.
9. Loer HLH, Turk D, Gomez-Mantilla JD, Selzer D, Lehr T. Physiologically based pharmacokinetic (PBPK) modeling of clopidogrel and its four relevant metabolites for CYP2B6, CYP2C8, CYP2C19, and CYP3A4 drug-drug-gene interaction predictions. *Pharmaceutics*. 2022;14:915.
10. Xu RJ, Kong WM, An XF, Zou JJ, Liu L, Liu XD. Physiologically-based pharmacokinetic-pharmacodynamics model characterizing CYP2C19 polymorphisms to predict clopidogrel pharmacokinetics and its anti-platelet aggregation effect following oral administration to coronary artery disease patients with or without diabetes. *Front Pharmacol*. 2020;11:593982.
11. Jiang XL, Samant S, Lesko LJ, Schmidt S. Clinical pharmacokinetics and pharmacodynamics of clopidogrel. *Clin Pharmacokinet*. 2015;54:147-166.
12. Hollopeter G, Jantzen HM, Vincent D, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature*. 2001;409:202-207.
13. Murugappa S, Kunapuli SP. The role of ADP receptors in platelet function. *Front Biosci*. 2006;11:1977-1986.

14. Dorsam RT, Murugappan S, Ding Z, Kunapuli SP. Clopidogrel: interactions with the P2Y12 receptor and clinical relevance. *Hematology*. 2003;8:359-365.
15. Collet JP. Current concepts in the clinical utility of platelet reactivity testing. *Interv Cardiol*. 2013;8:100-106.
16. Mazzeffi MA, Lee K, Taylor B, Tanaka KA. Perioperative management and monitoring of antiplatelet agents: a focused review on aspirin and P2Y(12) inhibitors. *Korean J Anesthesiol*. 2017;70:379-389.
17. Clopidogrel. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases. 2012.
18. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. *Semin Thromb Hemost*. 1999;25:15-19.
19. Zeymer U. Oral antiplatelet therapy in acute coronary syndromes: recent developments. *Cardiol Ther*. 2013;2:47-56.
20. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. *Clin Pharmacol Ther*. 2022;112:959-967.
21. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*. 2013;382:614-623.
22. Alvitigala BY, Gooneratne LV, Constantine GR, Wijesinghe R, Arawwawala L. Pharmacokinetic, pharmacodynamic, and pharmacogenetic assays to monitor clopidogrel therapy. *Pharmacol Res Perspect*. 2020;8:e00686.
23. Patel NK, Subbaiah G, Shah H, Kundlik M, Shrivastav PS. Rapid LC-ESI-MS-MS method for the simultaneous determination of clopidogrel and its carboxylic acid metabolite in human plasma. *J Chromatogr Sci*. 2008;46:867-875.
24. Peer CJ, Spencer SD, VanDenBerg DA, Pacanowski MA, Horenstein RB, Figg WD. A sensitive and rapid ultra HPLC-MS/MS method for the simultaneous detection of clopidogrel and its derivatized active thiol metabolite in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2012;880:132-139.
25. Grenier E, Louvet V, Vigneaux P. Parameter estimation in nonlinear mixed effects models with SAEM algorithm: extension from ODE to PDE. *ESAIM: Math Model Num*. 2014;48:1303-1329.
26. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. *AAPS J*. 2009;11:371-380.
27. Zhang L, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. *J Pharmacokinet Pharmacodyn*. 2003;30:387-404.
28. Bach T, Murry DJ, Stebounova LV, Deye G, Winokur P, An G. Population pharmacokinetic model of oxfendazole and metabolites in healthy adults following single ascending doses. *Antimicrob Agents Chemother*. 2021;65:e02129-20
29. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth*. 2004;92:208-217.
30. Pei Q, Huang L, Huang J, et al. Influences of CYP2D6(*)10 polymorphisms on the pharmacokinetics of iloperidone and its metabolites in Chinese patients with schizophrenia: a population pharmacokinetic analysis. *Acta Pharmacol Sin*. 2016;37:1499-1508.
31. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. *J Pharmacokinet Biopharm*. 1993;21:457-478.
32. Hutmacher MM, Kowalski KG. Covariate selection in pharmacometric analyses: a review of methods. *Br J Clin Pharmacol*. 2015;79:132-147.
33. Corliss BM, Polifka AJ, Harris NS, Hoh BL, Fox WC. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: comparing results of the VerifyNow P2Y12 assay to thromboelastography with platelet mapping. *J Neurosurg*. 2018;129:1160-1165.
34. Daou B, Starke RM, Chalouhi N, et al. P2Y12 reaction units: effect on hemorrhagic and thromboembolic complications in patients with cerebral aneurysms treated with the pipeline embolization device. *Neurosurgery*. 2016;78:27-33.
35. Petersson KJ, Hanze E, Savic RM, Karlsson MO. Semiparametric distributions with estimated shape parameters. *Pharm Res*. 2009;26:2174-2185.
36. Dean L, Kane M. Clopidogrel therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, eds. *Medical Genetics Summaries*. National Center for Biotechnology Information; 2012.
37. Collet JP, Hulot JS, Anzaha G, et al. High doses of clopidogrel to overcome genetic resistance: the randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). *JACC Cardiovasc Interv*. 2011;4:392-402.
38. Aleil B, Jacquemin L, De Poli F, et al. Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. *JACC Cardiovasc Interv*. 2008;1:631-638.
39. Mega JL, Hochholzer W, Frelinger AL 3rd, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA*. 2011;306:2221-2228.
40. Su Y, Cheng X, Dong Q. Dual antiplatelet therapy of clopidogrel and aspirin in secondary prevention of ischemic stroke: evidence and indications. *CNS Neurosci Ther*. 2015;21:870-876.
41. Lomakin N, Rudakova A, Buryachkovskaya L, Serebruany V. Cost-effectiveness of platelet function-guided strategy with clopidogrel or ticagrelor. *Eur Cardiol Rev*. 2019;14:175-178.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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