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RESEARCH ARTICLE

Physiologically based pharmacokinetic (PBPK) modeling to predict the pharmacokinetics of irbesartan in different *CYP2C9* genotypes

Chang-Keun Cho[1] · Pureum Kang[1] · Choon-Gon Jang[1] · Seok-Yong Lee[1] · Yun Jeong Lee[2] · Chang-Ik Choi[3]

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Abstract

Irbesartan, a potent and selective angiotensin II type-1 (AT_1) receptor blocker (ARB), is one of the representative medications for the treatment of hypertension. Cytochrome P450 (CYP) 2C9 is primarily involved in the oxidation of irbesartan. CYP2C9 is highly polymorphic, and genetic polymorphism of this enzyme is the leading cause of significant alterations in the pharmacokinetics of irbesartan. This study aimed to establish the physiologically based pharmacokinetic (PBPK) model to predict the pharmacokinetics of irbesartan in different *CYP2C9* genotypes. The irbesartan PBPK model was established using the PK-Sim® software. Our previously reported pharmacogenomic data for irbesartan was leveraged in the development of the PBPK model and collected clinical pharmacokinetic data for irbesartan was used for the validation of the model. Physicochemical and ADME properties of irbesartan were obtained from previously reported data, predicted by the modeling software, or optimized to fit the observed plasma concentration–time profiles. Model evaluation was performed by comparing the predicted plasma concentration–time profiles and pharmacokinetic parameters to the observed results. Predicted plasma concentration–time profiles were visually similar to observed profiles. Predicted AUC_{inf} in *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes were increased by 1.54- and 1.62-fold compared to *CYP2C9*1/*1* genotype, respectively. All fold error values for AUC and C_{max} in non-genotyped and *CYP2C9* genotyped models were within the two-fold error criterion. We properly established the PBPK model of irbesartan in different *CYP2C9* genotypes. It can be used to predict the pharmacokinetics of irbesartan for personalized pharmacotherapy in individuals of various races, ages, and *CYP2C9* genotypes.

Keywords Antihypertensive pharmacotherapy · CYP2C9 · Physiologically based pharmacokinetic (PBPK) model · Irbesartan · Genetic polymorphism

Introduction

Hypertension is one of the major risk factors for a variety of cardiovascular diseases (CVDs) including heart failure, acute coronary syndrome, and atrial fibrillation, and cerebral stroke (Kjeldsen 2018). Hypertension is a globally prevalent disease, affecting approximately 1.28 billion people aged 30–79 years in 2019 (NCD Risk Factor Collaboration (NCD-RisC) 2021) and causing 12.8% of the total annual deaths worldwide (World Health Organization 2021). Nevertheless, blood pressure control using antihypertensive medications was adequately achieved in less than 50 percent of patients with hypertension (Cooper-DeHoff and Johnson 2016; Mann and Flack 2023). The inter-individual variability of the drug responses may be mainly attributed to genetic factors associated with the disposition of drugs, such as polymorphisms of drug-transporters (Shin et al. 2020; Magadmi et al. 2023; Jeong et al. 2023) and

Chang-Keun Cho and Pureum Kang contributed equally to this study.

✉ Seok-Yong Lee
sylee@skku.edu

✉ Chang-Ik Choi
cichoi@dongguk.edu

[1] School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

[2] College of Pharmacy, Dankook University, Cheonan 31116, Republic of Korea

[3] College of Pharmacy, Dongguk University-Seoul, Goyang 10326, Republic of Korea

drug-metabolizing enzymes (Lee et al. 2018; Byeon et al. 2019, 2023; Bae et al. 2020; Kim et al. 2022; Cho et al. 2023a, b; Kang et al. 2023), and non-genetic factors including age, body weight, gender, race, co-administered drugs, etc. (Weinshilboum 2003; Lee et al. 2019; Jung et al. 2020). Individualized therapy considering various factors that influence the antihypertensive drug response is needed to reduce adverse sequelae and achieve proper therapeutic effects.

Irbesartan, a potent and selective angiotensin II type-1 (AT_1) receptor blocker (ARB), is one of the representative medications for the treatment of hypertension (Marino and Vachharajani 2001). Glucuronide conjugation (Perrier et al. 1994) and oxidation are the main metabolic pathways of irbesartan. Cytochrome P450 (CYP) 2C9 is primarily involved in the oxidation route, while CYP3A4 has a negligible contribution (Bourrié et al. 1999). Previous in vitro studies reported that the active hepatic uptake of irbesartan is mediated by organic anion-transporting polypeptide (OATP) 1B1 and 1B3 (Chapy et al. 2015; Izumi et al. 2018; McFeely et al. 2019). Irbesartan and its metabolites are excreted by both biliary and renal routes (Brunner 1997), with less than 2% of the dose as unchanged form in the urine (European Medicines Agency 2023).

CYP2C9 is highly polymorphic, and genetic polymorphism of this enzyme leads to significant alterations in the pharmacokinetics and pharmacodynamics of clinically used CYP2C9 substrate drugs (Perini et al. 2005; Bae et al. 2011a, 2012; Choi et al. 2011; Lee et al. 2016; Kim et al. 2017, 2022). To date, more than 85 different *CYP2C9* allelic variants and subvariants (*CYP2C9*1B* to **85*) have been identified (https://www.pharmvar.org/gene/CYP2C9). Of these alleles, *CYP2C9*2* (rs1799853, c.430C > T, p.Arg144Cys) and *CYP2C9*3* (rs1057910, c.1075A > C, p.Ile359Leu), the two most common alleles (Daly et al. 2017), exhibit impaired catalytic activity compared to the normal allele both in vitro and in vivo (Tang et al. 2001; Lee et al. 2003; Perini et al. 2005). *CYP2C9*13* (rs72558187, c.269 T > C, p.Leu90Pro), an allele only observed in East Asians with an extremely low frequency of 0.2–0.7% (Bae et al. 2011b; Daly et al. 2017), also shows reduced enzyme activity (Guo et al. 2005; Wang et al. 2015). Thus, dose adjustment of irbesartan according to genetic variations of individuals could be recommended for optimal antihypertensive therapy.

The physiologically based pharmacokinetic (PBPK) model, a mechanistic approach to describe the pharmacokinetics of xenobiotics, is widely used to estimate drug exposures in special populations such as pediatrics, pregnant women, obesity, and those with organ impairments (Kuepfer et al. 2016; Zhuang and Lu 2016; Marsousi et al. 2017). The PBPK model also aids in scrutinizing the pharmacokinetic alterations according to drug-drug interactions (Min and Bae 2017) and the effects of genetic polymorphisms (Cho et al. 2021b; Lee et al. 2022; Rüdesheim et al. 2022; Yang et al. 2022). Previously, PBPK models of irbesartan focused on oral absorption (Kaur et al. 2020) and hepatic uptake (Chapy et al. 2015) have been reported. However, no study has examined the effect of irbesartan according to *CYP2C9* genetic polymorphism. In this study, we aimed to establish the PBPK model of irbesartan in different *CYP2C9* genotypes.

Methods

Software

PK-Sim® version 10.0 (Bayer AG, Leverkusen, Germany) was used for the building of the irbesartan PBPK model, sensitivity analysis, and parameter optimization. Plasma concentration–time profiles in previous publications were digitized using Engauge Digitizer® version 12.1 (https://markummitchell.github.io/engauge-digitizer/). Pharmacokinetic parameters that were not extracted from previous publications were estimated via non-compartmental analysis (NCA) using the BA Calc 2007 analysis program (MFDS, Cheongju, Republic of Korea) based on the obtained plasma concentration–time profiles.

Clinical pharmacokinetic data

Our previously reported pharmacogenomic data in which 150 mg single oral dose of irbesartan was administered in healthy Korean subjects with three different genotype groups (Choi et al. 2012) was used for the development (to determine input parameters) of the PBPK model. Clinical pharmacokinetic studies were extensively investigated and the pharmacokinetic data with single and multiple oral dose administrations of irbesartan in healthy adults under fasting state were collected and used for the validation (to verify the developed model) of the PBPK model.

Model building

The "middle-out" strategy was used for the PBPK model building. Previously reported literature or drug databases were extensively investigated to obtain the physicochemical and absorption, distribution, metabolism, and excretion (ADME) characteristics of irbesartan, thereafter incorporating them into the PBPK model. Of those, Log P and pK_a were adjusted within the previously reported ranges. Gastric emptying time was assigned as 40 min based on Klingensmith et al. (2010). The specific intestinal and organ permeabilities were optimized and calculated by the quantitative structure–activity relationship (QSAR) method built in the PK-Sim® software, respectively.

CYP2C9 and UDP-glucuronosyltransferase (UGT) 1A3 enzymes were incorporated to reflect the metabolism of irbesartan. Michaelis–Menten constant (K_m) values for CYP2C9 and UGT1A3 were obtained from Bourrié et al. (1999) and Chapy et al. (2015) respectively, and the value for CYP2C9 was minorly modified. Turnover number (k_{cat}) values of CYP2C9 and UGT1A3 for the non-genotyped model were simultaneously optimized to recover the mean observed plasma concentration–time profile obtained from our pharmacogenomic study (Choi et al. 2012). Thereafter, the developed non-genotyped model was scaled to the PBPK model for different *CYP2C9* genotypes, where the k_{cat} values in different *CYP2C9* genotypes were optimized to describe the plasma concentration–time profiles for each genotype in Choi et al. (2012). The OATP1B1 and 1B3 were incorporated to describe the transport of irbesartan. The k_{cat} and K_m values for OATP1B1 and 1B3 were optimized and obtained from Chapy et al. (2015), respectively. The reference concentration of CYP2C9 was 3.84 µmol/L (Rodrigues 1999) and UGT1A3, OATP1B1, and 1B3 were 1.00 µmol/L, the default value of PK-Sim®. Relative expression values for CYP2C9 and UGT1A3 were obtained from the reverse transcription-polymerase chain reaction (RT-PCR) data (Nishimura et al. 2003; Nishimura and Naito 2005, 2006) and values for OATPs were obtained from ArrayExpress data (http://www.ebi.ac.uk/microarray-as/ae/).

Dissolution characteristics were described using the Lint80 function and the dissolution time was extracted from the dissolution profile of the commercial product (Khullar et al. 2015). Model input parameters were refined by iteratively performing sensitivity analysis and parameter identification based on the observed data at each step and the Levenberg–Marquardt algorithm was adopted for parameter optimization. Estimation methods for the partition coefficients and cellular permeabilities were Poulin and Theil (Poulin and Theil 2000; Poulin et al. 2001; Poulin and Theil 2002a, b) and Charge dependent Schmitt normalized to PK-Sim® (Hindmarsh et al. 2023), respectively.

Table 1 Demographic and dose administration information of clinical studies used to build the non-genotyped PBPK model of irbesartan

References	Dose	n	Demographic data		
			Female (%)	Age (years)	Weight (kg)
Choi et al. (2012)[a]	150 mg SD	28	0	23.5 ± 1.2	63.8 ± 5.8
El-Desoky et al. (2011)	150 mg SD	2	0	45–50	–
Huang et al. (2006)	150 mg SD	18	0	18–25	55.9–72.6
Marino et al. (1998a)	150 mg SD	9	0	24–38	66.0–85.0
Bae et al. (2009)	300 mg SD	23	0	22–38	63–76
Huang et al. (2006)	300 mg SD	18	0	19–27	61.2–75.3
Marino et al. (1998a)	300 mg SD	9	0	22–32	68.5–86.0
Marino et al. (1998b)	300 mg SD	10	30	55 ± 10.6	74.5 ± 8.1
Marino et al. (1998a)	600 mg SD	9	0	26–45	64.0–96.5
Marino et al. (1998a)	900 mg SD	9	0	20–45	67.5–96.2
Marino et al. (1998a)	150 mg daily	9	0	24–38	66.0–85.0
Choi et al. (2015)	300 mg daily	25	0	25.9 ± 3.8	67.8 ± 6.0
Marino et al. (1998a)	300 mg daily	9	0	22–32	68.5–86.0
Marino et al. (1998b)	300 mg daily	10	30	55 ± 10.6	74.5 ± 8.1
Marino et al. (1998a)	600 mg daily	9	0	26–45	64.0–96.5
Marino et al. (1998a)	900 mg daily	9	0	20–45	67.5–96.2

Age and weight data are expressed as the mean ± standard deviation or range (min–max)

SD single dose, *daily* once daily dose, *n* number of subjects, – not given

[a]Data used for the model development

Table 2 Demographic, genotype, and dose administration information of clinical studies used to build the irbesartan PBPK model in different *CYP2C9* genotypes

References	Dose	CYP2C9	n	Demographic data		
				Female (%)	Age (years)	Weight (kg)
Choi et al. (2012)	150 mg SD	**1/*1*	12	0	23.8 ± 0.6	64.9 ± 5.9
Choi et al. (2012)	150 mg SD	**1/*3*	10	0	23.0 ± 1.6	62.9 ± 6.1
Choi et al. (2012)	150 mg SD	**1/*13*	6	0	24.3 ± 2.3	65.8 ± 6.1

Age and weight data are expressed as the mean ± standard deviation

SD single dose, *n* number of subjects

Table 3 Input parameters for the irbesartan PBPK model

Parameter (unit)	Reference value	Input value	References/comments
Basic physico-chemistry			
Molecular weight (g/mol)	428.53	428.53	DrugBank
Log P	1–5.39	2.7	Sanofi and DrugBank
pK_a	4.9–6.1 (Acidic) 4.12 (Basic)	5.80 (Acidic) 4.12 (Basic)	Cagigal et al. (2001), DrugBank, and Chapy et al. (2015)
f_u (%)	10.0	10.0	DrugBank
Solubility at reference pH 1.2 (mg/mL)	1.29	1.29	Kaur et al. (2020)
Absorption			
Specific intestinal permeability (cm/min)	–	$3.19E^{-4}$	Optimized by PK-Sim®
Distribution			
Specific organ permeability (cm/min)	–	$2.33E^{-3}$	Calculated by PK-Sim®
Metabolism			
CYP2C9 K_m (μM)	54.0	57.0	Bourrié et al. (1999), minor modification
CYP2C9 k_{cat} (1/min) *Non-genotyped*	–	27.6	Optimized by PK-Sim®
CYP2C9 k_{cat} (1/min) *CYP2C9*1/*1*	–	33	Optimized by PK-Sim®
CYP2C9 k_{cat} (1/min) *CYP2C9*1/*3*		11	Optimized by PK-Sim®
CYP2C9 k_{cat} (1/min) *CYP2C9*1/*13*		10	Optimized by PK-Sim®
UGT1A3 K_m (μM)	368.6	368.6	Chapy et al. (2015)
UGT1A3 k_{cat} (1/min)	–	30	Optimized by PK-Sim®
Transport			
OATP1B1 K_m (μM)	0.69	0.69	Chapy et al. (2015)
OATP1B1 k_{cat} (1/min)	–	1.0	Optimized by PK-Sim®
OATP1B3 K_m (μM)	11.09	11.09	Chapy et al. (2015)
OATP1B3 k_{cat} (1/min)	–	0.3	Optimized by PK-Sim®
Excretion			
Renal plasma clearance (mL/min/kg)	–	0.01	Optimized by PK-Sim®
Biliary plasma clearance (L/hr/kg)	–	0.02	Optimized by PK-Sim®
Formulation			
Dissolution time (min)	< 20	10	Khullar et al. (2015)

Log P logarithm of octanol/water partition coefficient, pK_a negative logarithm of acid dissociation constant, f_u fraction unbound in plasma, K_m Michaelis–Menten constant, k_{cat} turnover number

Sensitivity analysis

A sensitivity analysis was performed to confirm which input parameters had an impact on the area of the plasma concentration–time curve from 0 to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) of irbesartan. Input parameters that were optimized, related to optimized parameters, or might have a marked influence on calculation methods used in the model, were included in the analysis. The sensitivity was calculated as follows (Eq. 1):

$$S = \frac{\Delta PK}{PK} \div \frac{\Delta p}{p} \quad (1)$$

where S is the sensitivity, PK is the initial value of the pharmacokinetic parameter, ΔPK is the change of the pharmacokinetic parameter from initial value, p is the initial value of the examined parameter, and Δp is the change of the examined parameter from initial value. A sensitivity of + 1.0 indicates that a + 10% change in an examined input parameter causes a + 10% change in the predicted pharmacokinetic parameter.

Model evaluation

Both graphical and numerical evaluation methods were used to evaluate the PBPK model. Predicted plasma concentration–time profiles plotting the arithmetic mean and 90%

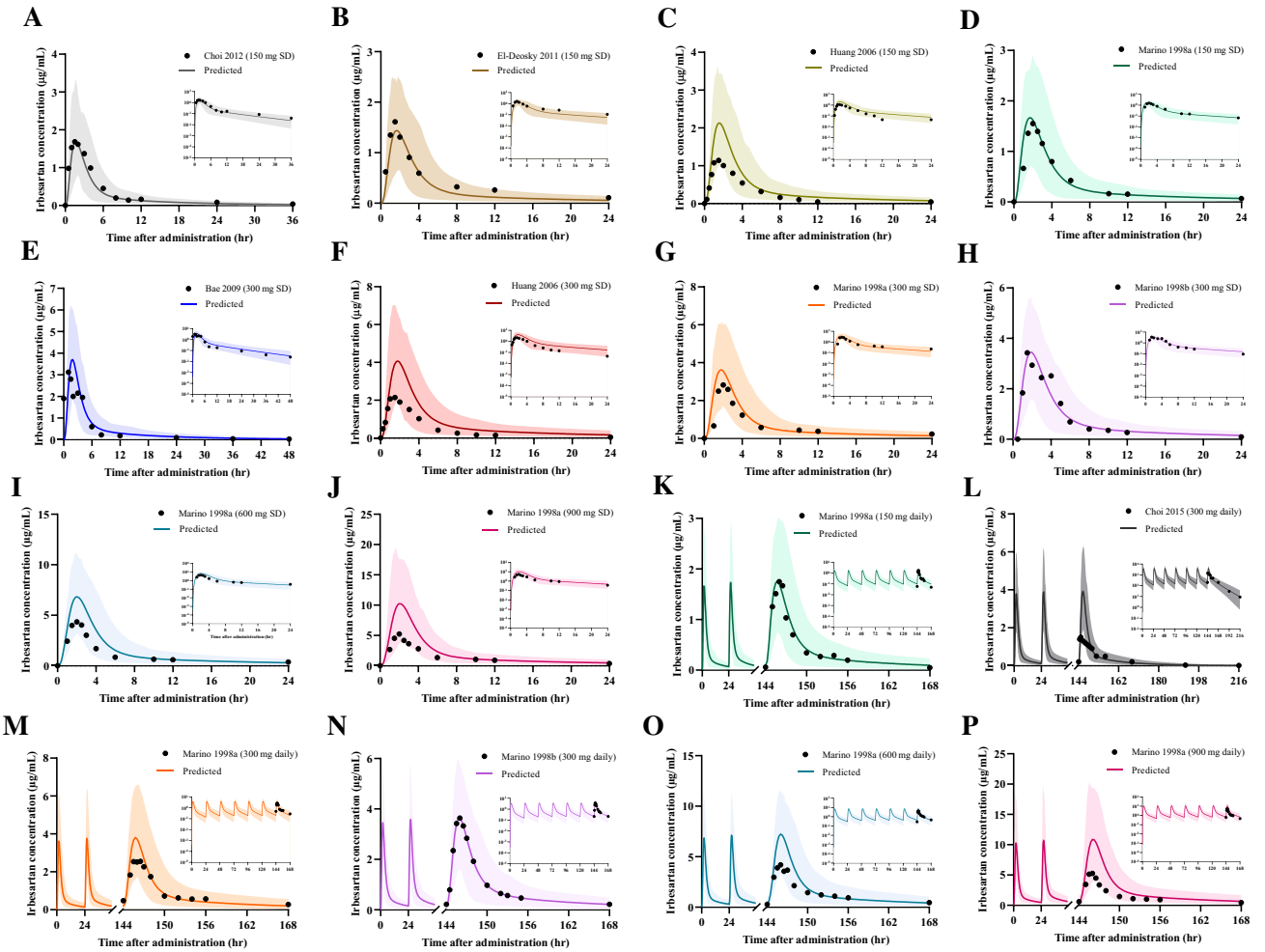

Fig. 1 Predicted and observed plasma concentration–time profiles of irbesartan after **A–J** single (**A** development) and **K–P** multiple oral doses in non-genotyped populations. Solid lines and shaded areas indicate arithmetic mean and 90% prediction interval (5th and 95th percentile range) of predicted plasma concentrations, respectively. Circles indicate the mean of observed plasma concentrations. Profiles are shown as linear and semi-logarithmic scale. *SD* single dose, *daily* once daily dose

prediction interval (i.e. 5th and 95th percentile range) for the virtual population (n = 100) with close demographic characteristics to those of the subject populations in clinical studies were visually compared to the observed profiles. The demographic data not reported in previous studies were generated based on the implemented algorithm in the PK-Sim® software. A two-fold error criterion for AUC and C_{max}, commonly used in previous studies (Abduljalil et al. 2015; Sager et al. 2015), was used as the numerical evaluation criterion. The fold error value was calculated as follows (Eq. 2):

$$\text{Fold error} = \frac{\text{Predicted value}}{\text{Observed value}} \tag{2}$$

To quantitatively measure the model's predictive performance, the mean relative deviation (MRD) of all predicted plasma concentrations and the geometric mean fold error (GMFE) for predicted AUC and C_{max} were calculated according to Eqs. 3 and 4, respectively:

$$\text{MRD} = 10^{x}, \text{with } x = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(\log_{10}C_{pred,i} - \log_{10}C_{obs,i})^2} \tag{3}$$

where $C_{pred,i}$ is the i-th predicted plasma concentration, $C_{obs,i}$ is the corresponding observed plasma concentration, and N is the number of observations.

$$\mathrm{GMFE} = 10^{x},\ \text{with } x = \frac{1}{n}\sum_{i=1}^{n}\left|\log_{10}\left(\frac{PK_{pred,i}}{PK_{obs,i}}\right)\right| \quad (4)$$

where $PK_{pred,i}$ is the i-th predicted AUC or C_{max} value, $PK_{obs,i}$ is the corresponding observed value, and n is the number of the collected pharmacokinetic parameter data.

Results

Model building and evaluation

A total of nineteen clinical pharmacokinetic data, consisting of four data for development (our pharmacogenomic data) and fifteen data for validation (collected data from previous publications), were used to build the PBPK model. Of those, sixteen data were used in the non-genotyped model (Table 1) and three data were used in the genotyped model (Table 2). The demographic, genotype, and dose administration information of clinical studies used to build the irbesartan model are presented in Tables 1 and 2. Input parameters for the irbesartan PBPK model are summarized in Table 3.

The comparison between the predicted and observed plasma concentration–time profiles after single or multiple oral doses of irbesartan at 150–900 mg dose range is visualized in Fig. 1**.** All fold error values for AUC and C_{max} in the non-genotyped model were included within the two-fold range criterion, with respective ranges being 0.52–1.95 and 0.83–1.94 (Fig. 2A and B). GMFE for AUC was 1.30 and 62.5% (10/16) and 75.0% (12/16) of fold error values for AUC were within the 1.25-fold and

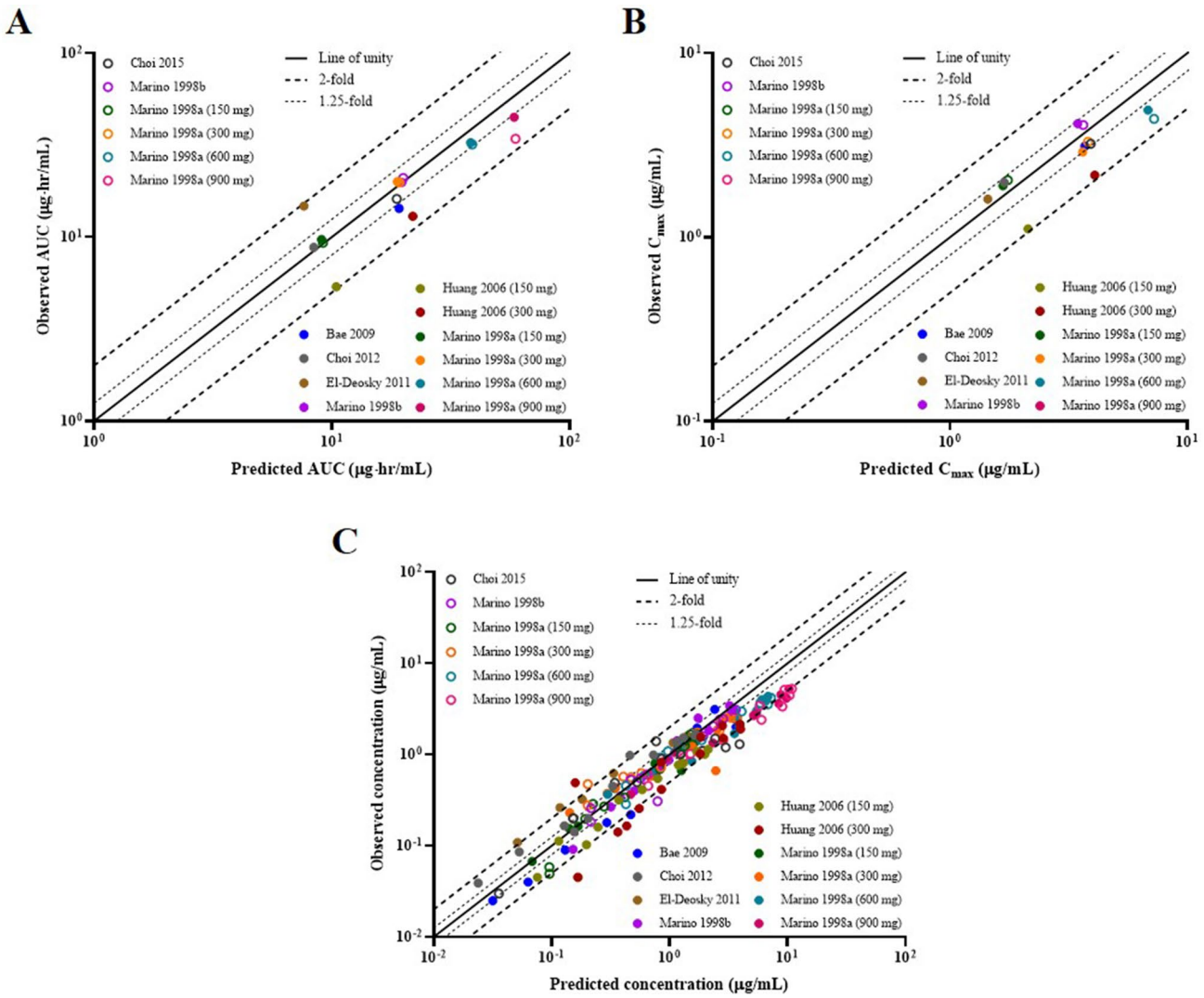

Fig. 2 Goodness-of-fit plots comparing the predicted versus observed **A** AUC **B** C_{max} and **C** plasma concentration of irbesartan in non-genotyped populations. Closed circles indicate single dose administrations and open circles indicate multiple dose administrations. Solid lines indicate the line of unity, dashed lines indicate the two-fold range and dotted lines indicate the 1.25-fold range

Table 4 Comparison between the predicted and observed AUC, C_{max}, and plasma concentration values after single or multiple oral doses of irbesartan in non-genotyped populations

References	Dose	AUC (μg·h/mL)[a]			C_{max} (μg/mL)[b]			MRD
		Observed	Predicted	Fold error	Observed	Predicted	Fold error	
Choi et al. (2012)[c]	150 mg SD	8.78[d]	8.40	0.96	1.99[d]	1.69	0.85	1.40
El-Desoky et al. (2011)	150 mg SD	14.75	7.63	0.52	1.61	1.44	0.89	1.60
Huang et al. (2006)	150 mg SD	5.36	10.43	1.95	1.11	2.13	1.92	1.79
Marino et al. (1998a)	150 mg SD	9.70	9.05	0.93	1.90	1.67	0.88	1.25
Bae et al. (2009)	300 mg SD	14.3	19.2	1.34	3.12	3.70	1.18	1.50
Huang et al. (2006)	300 mg SD	12.96	21.90	1.69	2.17	4.07	1.88	2.16
Marino et al. (1998a)	300 mg SD	20.00	18.86	0.94	2.90	3.62	1.25	1.64
Marino et al. (1998b)	300 mg SD	19.81	19.70	0.99	4.14	3.45	0.83	1.27
Marino et al. (1998a)	600 mg SD	32.60	38.33	1.18	4.90	6.83	1.39	1.58
Marino et al. (1998a)	900 mg SD	44.80	58.39	1.30	5.30	10.25	1.93	1.82
Marino et al. (1998a)	150 mg daily	9.30	9.16	0.98	2.04	1.75	0.86	1.31
Choi et al. (2015)	300 mg daily	16.12	18.73	1.16	3.22	3.91	1.22	1.65
Marino et al. (1998a)	300 mg daily	19.80	19.2	0.97	3.30	3.81	1.15	1.43
Marino et al. (1998b)	300 mg daily	20.92	19.96	0.95	4.07	3.64	0.89	1.34
Marino et al. (1998a)	600 mg daily	31.90	38.89	1.22	4.40	7.23	1.64	1.49
Marino et al. (1998a)	900 mg daily	34.20	59.18	1.73	5.60	10.87	1.94	1.89

Observed and predicted data are given as the mean

[a]AUC_{inf} single dose, $AUC_{\tau,ss}$ multiple dose

[b]C_{max} single dose, $C_{max,ss}$ multiple dose

[c]Data used for the model development

[d]Calculated by non-compartmental analysis

AUC_{inf} area under the plasma concentration–time curve from 0 to infinity, *$AUC_{\tau,ss}$* area under the plasma concentration–time curve over the dosing interval at steady state, *C_{max}* maximum plasma concentration, *$C_{max,ss}$* maximum plasma concentration over the dosing interval at steady state, *MRD* mean relative deviation, *SD* single dose, *daily* once daily dose

1.5-fold range, respectively. For C_{max}, 62.5% (10/16) and 68.8% (11/16) of the predicted values were included in the 1.25-fold and 1.5-fold range of the corresponding observed values, respectively, and GMFE was 1.40. As illustrated in the goodness-of-fit plot in Fig. 2C, the percentage of the predicted plasma concentrations within the 1.25- and two-fold range of the observed plasma concentrations were 41.5% and 86.9%, respectively, with an overall MRD of 1.57. The detailed results are presented in Table 4.

The comparison between the predicted and observed plasma concentration–time profiles in different *CYP2C9* genotypes is shown in Fig. 3. Predicted profiles for three different genotypes were visually similar to the observed profiles. Predicted AUC_{inf} in *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes were increased by 1.54- and 1.62-fold compared to *CYP2C9*1/*1* genotype, respectively. Predicted C_{max} for the population with the *CYP2C9*3* and **13* carriers were 1.27- and 1.28-fold higher than the wild-type carrier, respectively. Goodness-of-fit plots for AUC_{inf} (Fig. 4A) and C_{max} (Fig. 4B) in the irbesartan model related to *CYP2C9* genetic polymorphism exhibited that the predicted values were almost consistent with their corresponding observed values with all fold error values included in the 1.25-fold range (AUC_{inf} range 0.98–1.09, C_{max} range 0.93–1.14). GMFE for AUC_{inf} was 1.04 and for C_{max} was 1.08. As visualized in Fig. 4C, 58.3% and 94.4% of fold error values for plasma concentrations were included in the 1.25- and two-fold range, respectively, and overall MRD was 1.37. The detailed results are presented in Table 5.

Sensitivity analysis

The results of the sensitivity analysis are illustrated in Fig. 5. Input parameters with sensitivity values calculated as greater than 0.5 were considered sensitive. Sensitive input parameters for AUC_{inf} and C_{max} of irbesartan were as follows, in order of higher to lower impact; lipophilicity, acidic pK_a, administered dose, and fraction unbound were sensitive input parameters to AUC_{inf} of irbesartan. Lipophilicity and dose were sensitive input parameters to the C_{max} of irbesartan.

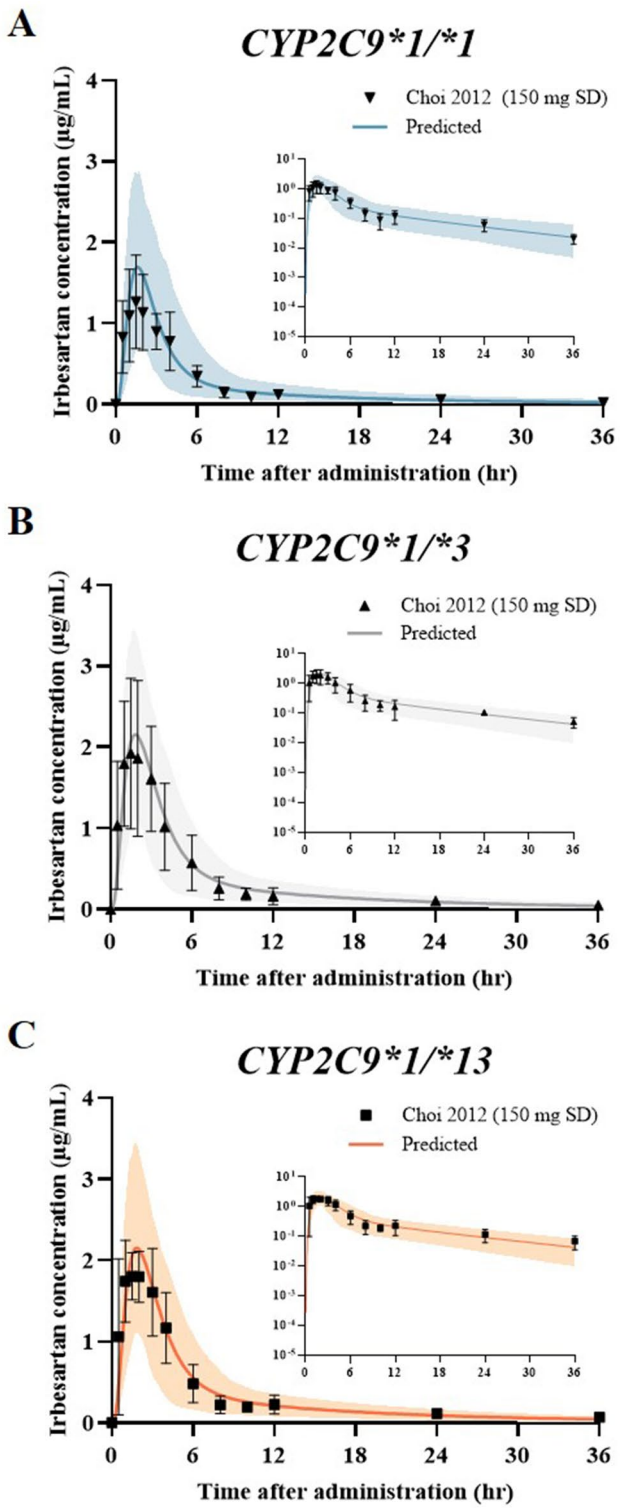

Fig. 3 Predicted and observed plasma concentration–time profiles of irbesartan after 150 mg single oral dose in **A** *CYP2C9*1/*1*, **B** *CYP2C9*1/*3*, and **C** *CYP2C9*1/*13* genotypes. Solid lines and shaded areas indicate arithmetic mean and 90% prediction interval (5th and 95th percentile range) of predicted plasma concentrations, respectively. Symbols (inverted triangle; *CYP2C9*1/*1*, triangle; **1/*3*, and rectangle; **1/*13*) and error bars indicate the mean and standard deviation of observed plasma concentrations, respectively. Profiles are shown as linear and semi-logarithmic scale. *SD* single dose

Discussion

Genetic polymorphism of drug-metabolizing enzymes and transporters is one of the principal issues in achieving adequate control of blood pressure using antihypertensive agents (Oliveira-Paula et al. 2019). Concurrently, several factors including age, gender, and obesity are the potential indicators that could contribute to the inter-individual variations of antihypertensive response (Chapman et al. 2002; Hiltunen et al. 2007). PBPK modeling enables the prediction of the pharmacokinetics of drugs simultaneously considering all of the characteristics mentioned above, and therefore, it may be a desirable approach for the implementation of individualized pharmacotherapy in each patient (Kim et al. 2018, 2021; Cho et al. 2021a, b, 2022; Whang et al. 2022). To date, there have been several attempts to establish the PBPK models in populations with different genotypes for antihypertensive agents such as candesartan (Jung et al. 2021), losartan (Tanveer et al. 2022), and metoprolol (Rüdesheim et al. 2020).

In the present study, a whole-body PBPK model of irbesartan according to *CYP2C9* genetic polymorphism was appropriately established. All predicted AUC and C_{max} values in the non-genotyped populations and different *CYP2C9* genotypes were within the two-fold range of the observed values and calculated GMFE and MRD values showed a good predictive performance. The developed model properly predicted the irbesartan pharmacokinetics in different demographic characteristics and oral dose administrations and it also captured the previous finding in which AUC_{inf} and C_{max} of the *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes were significantly higher than the *CYP2C9*1/*1* genotype (Choi et al. 2012). This suggests the present model could be applied to predict the pharmacokinetics of irbesartan after single and multiple dose administrations with a dose range of 150–900 mg/d in healthy subjects with different *CYP2C9* genotypes.

Extensive prior knowledge of ADME and drug-dependent properties of irbesartan were consolidated in this PBPK model. In the metabolism of irbesartan, CYP2C9 is the only allocated enzyme for the oxidation pathway due to the negligible effects of CYP3A4 (Bourrié et al. 1999). Likewise, the glucuronidation pathway was assumed to be mediated by UGT1A3 based on the fact that UGT1A3 is highly selective toward *N2*-glucuronidation of tetrazoles (Alonen et al. 2008) and irbesartan is metabolized to tetrazole-*N2*-glucuronide conjugate (Perrier et al. 1994; Chando et al. 1998). Metabolites of irbesartan are pharmacologically inactive (Gillis and Markham 1997), thereby the PBPK model for those was not established in this study. Both OATP1B1 and 1B3 transporters are known to be responsible for the hepatic uptake of irbesartan.

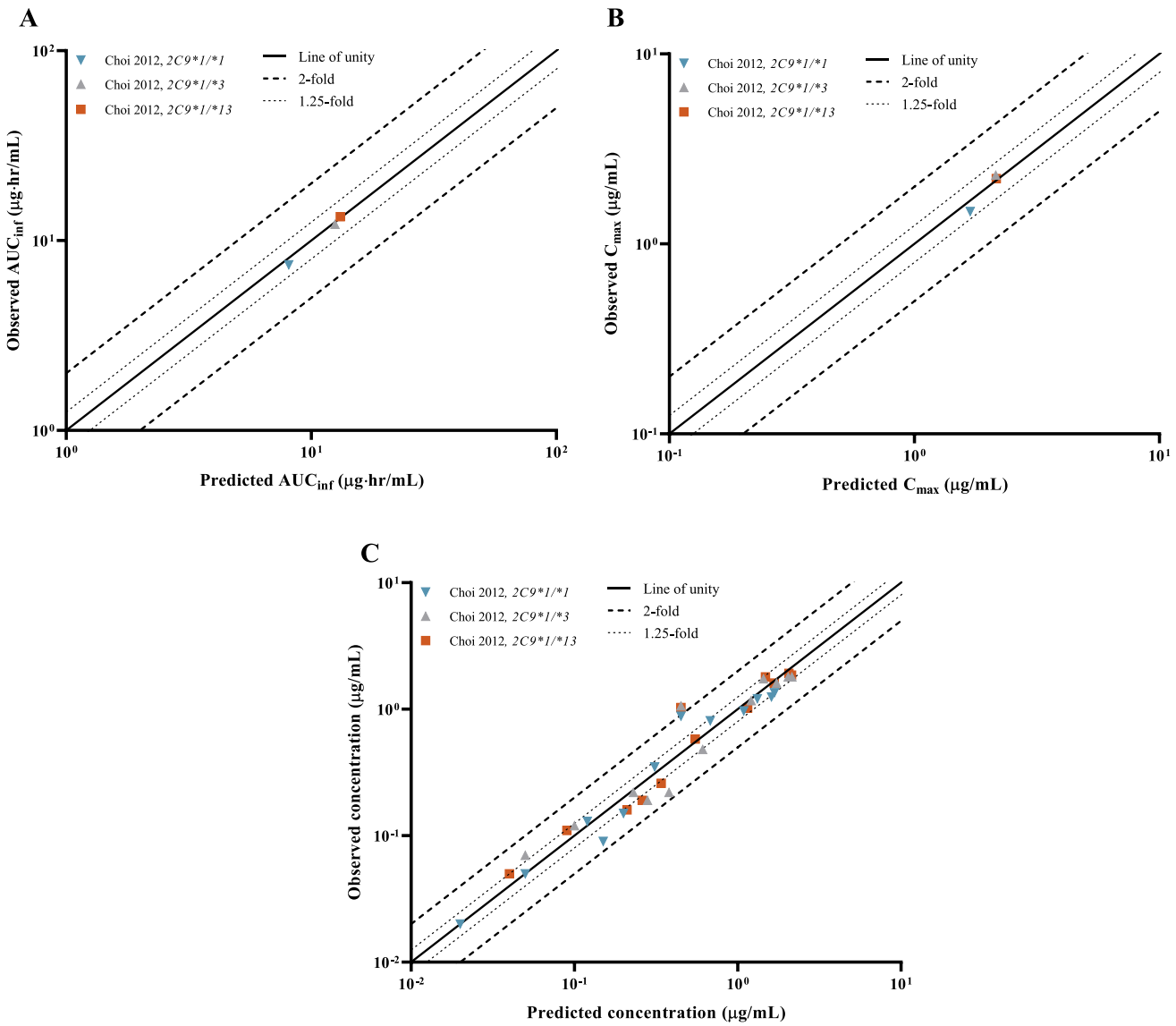

Fig. 4 Goodness-of-fit plots comparing the predicted versus observed **A** AUC_{inf} **B** C_{max} and **C** plasma concentration of irbesartan in different *CYP2C9* genotypes. Inverted triangle, triangle, and rectangle symbols indicate *CYP2C9*1/*1*, **1/*3*, and **1/*13* genotypes, respectively. Solid lines indicate the line of unity, dashed lines indicate the two-fold range and dotted lines indicate the 1.25-fold range

Table 5 Comparison between the predicted and observed AUC_{inf}, C_{max}, and plasma concentration values after 150 mg single oral dose of irbesartan in different *CYP2C9* genotypes

References	Dose	CYP2C9	AUC_{inf} (µg·h/mL)			C_{max} (µg/mL)			MRD
			Observed	Predicted	Fold error	Observed	Predicted	Fold error	
Choi et al. (2012)	150 mg SD	**1/*1*	7.45	8.1	1.09	1.48	1.69	1.14	1.34
Choi et al. (2012)	150 mg SD	**1/*3*	12.19	12.5	1.03	2.3	2.15	0.93	1.42
Choi et al. (2012)	150 mg SD	**1/*13*	13.35	13.13	0.98	2.21	2.16	0.98	1.35

AUC_{inf} area under the plasma concentration–time curve from 0 to infinity, *C_{max}* maximum plasma concentration, *MRD* mean relative deviation, *SD* single dose

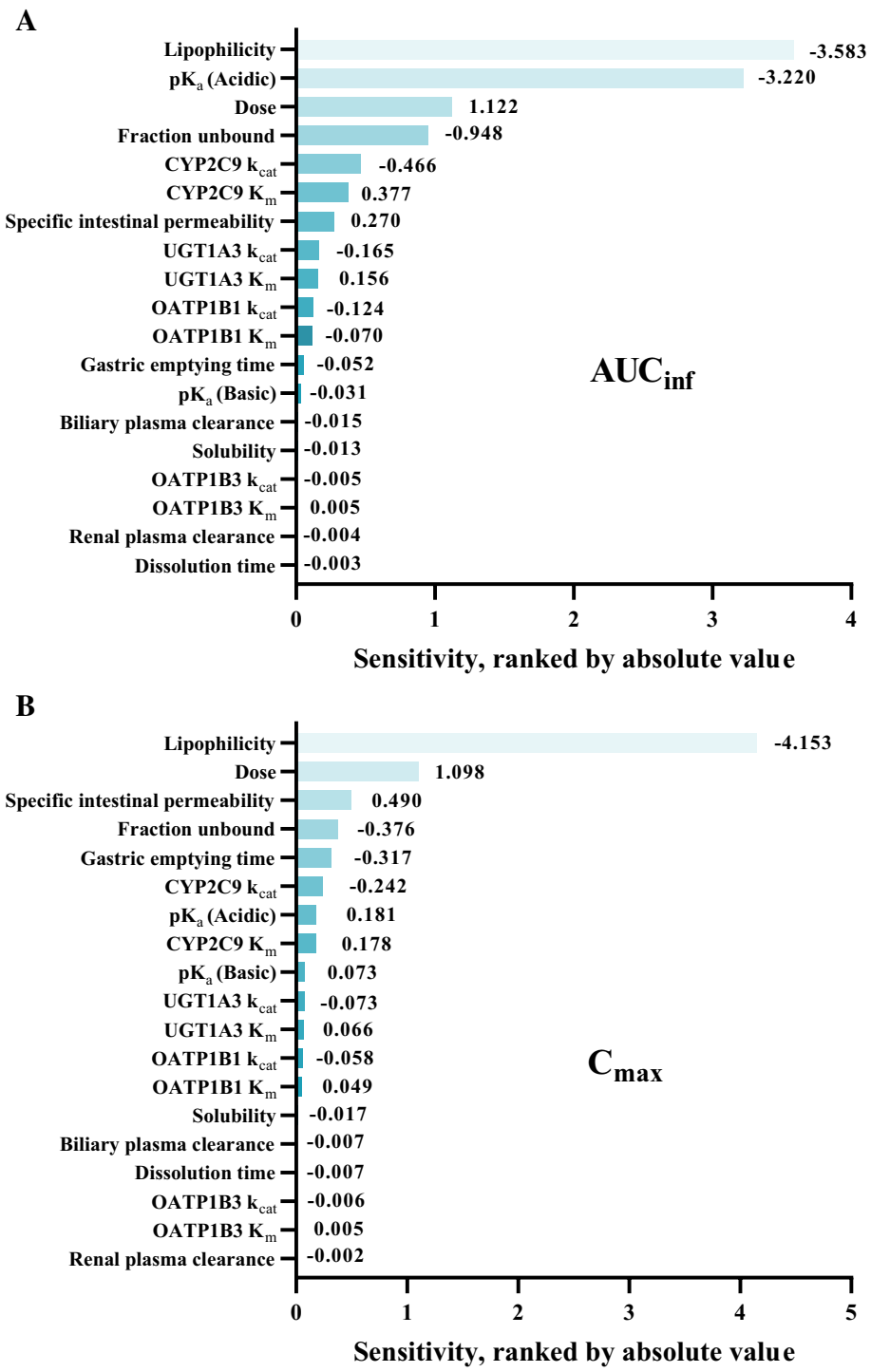

Fig. 5 Results of sensitivity analysis to single parameters, measured as the change of predicted **A** AUC_{inf} and **B** C_{max} following the administration of 150 mg single oral dose of irbesartan

Uptake contributions of OATP1B1 and 1B3 in our model are consistent with the previous in vitro studies in which the relative contribution of OATP1B1 is much higher than OATP1B3 (Chapy et al. 2015; Izumi et al. 2018).

A slight increase or stagnation of irbesartan plasma concentration was noted at 10–12 h after administration in our pharmacogenomic data (Choi et al. 2012), but the present model did not capture this phenomenon. Previous studies proposed that the phenomenon could be triggered by the enterohepatic circulation of irbesartan and its glucuronide metabolite (Davi et al. 2000; Chapy et al. 2015). Meanwhile, Karatza and Karalis (2020) suggested that there is a possibility that absorption complexities, representatively irregular gastric emptying time, may contribute to the double-peak of irbesartan and properly captured it using a population pharmacokinetic approach. To the best of our knowledge,

no irbesartan PBPK model has elucidated this phenomenon to date, including our study. PBPK models focusing on enterohepatic circulation and/or complex absorption kinetics could allow a more accurate capture of the plasma concentration–time profiles of irbesartan.

Five clinical studies have assessed the impact of *CYP2C9* genetic polymorphism on the pharmacokinetics and/or pharmacodynamics of irbesartan (Hallberg et al. 2002; Wen et al. 2003; Hong et al. 2005; Chen et al. 2006; Choi et al. 2012). Chen et al. (2006) and Hong et al. (2005) reported that plasma irbesartan concentration at 6 h after dosing in Chinese hypertensive patients carrying the *CYP2C9*3* allele variant was significantly higher than those carrying the wild-type allele. Choi et al. (2012) showed that *CYP2C9*3* and **13* alleles markedly altered the AUC, C_{max}, half-life ($t_{1/2}$), and apparent clearance (CL/F) of irbesartan in healthy Korean subjects. Chen et al. (2006) and Hallberg et al. (2002) reported a notable reduction of diastolic blood pressure (DBP) in Chinese hypertensive patients with *CYP2C9*1/*3* genotype and Swedish patients with *CYP2C9*1/*2* genotype, respectively. On the other hand, Wen et al. (2003) and Hong et al. (2005) reported that the impacts of the *CYP2C9*3* variant on the therapeutic efficacy of irbesartan were not significant. Although controversial results in the aspects of pharmacodynamics have been shown, it seems that the genetic polymorphism of *CYP2C9* may be one of the predictive indicators for the antihypertensive effects of irbesartan treatment. Among these studies, Choi et al. (2012), our previous pharmacogenomic study, was the only study that included the information to develop the PBPK model such as plasma concentration–time profiles and pharmacokinetic parameters including AUC and C_{max} according to *CYP2C9* genetic polymorphism. Accordingly, we developed the PBPK model for *CYP2C9*3* and **13* allele variants using these data (Choi et al. 2012), and the model for *CYP2C9*2* allele was not established because there was no available data in previous studies. Since the *CYP2C9*2* allele is the most frequently observed variant globally (Daly et al. 2017), further studies on this variant should be performed.

Albeit the importance of the *CYP2C9* genetic polymorphism on the pharmacokinetics or therapeutic efficacy of irbesartan, considerations for the genetic polymorphisms of *UGT* and *SLCO* genes may also be desirable. *UGT* gene is highly polymorphic with more than 200 allele variants identified and these variants are known to influence the expression levels and/or enzymatic activity of UGT (Stingl et al. 2014). The *SLCO* gene, encoding the OATP transporter, is also polymorphic, by which the efficacy and safety of OATP substrates are affected (Nakanishi and Tamai 2012). Previous studies have shown that the *UGT* and/or *SLCO* genetic polymorphisms could have a potential role in the inter-individual variations of the drug responses for some ARB class drugs (Suwannakul et al. 2008; Hirvensalo et al. 2020; Song et al. 2021). However, to our knowledge, the effects of genetic polymorphisms of *UGT* and *SLCO* genes on the plasma concentrations or antihypertensive responses of irbesartan have been not identified. Thus, we established the PBPK model of irbesartan associated with the *CYP2C9* genetic polymorphism in the present study. Future pharmacogenomic and PBPK modeling studies related to these genes may be needed.

In summary, we established the PBPK model of irbesartan, through which the pharmacokinetic alterations according to *CYP2C9* genetic polymorphism were properly described. The present model could contribute to personalized antihypertensive pharmacotherapy of irbesartan via pharmacokinetic predictions considering together the various causes related to the inter-individual variability of drug response.

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Declarations

Conflict of interest All authors declare no conflict of interest.

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