

A POPULATION PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF ROSUVASTATIN ACCORDING TO OATP1B1 AND BCRP POLYMORPHISMS IN YOUNG AND ELDERLY SUBJECTS

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BACKGROUNDS

- Rosuvastatin is one of the most hydrophilic statins (3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors) used for the treatment of hyperlipidemia.
- Rosuvastatin is taken up into the liver predominantly via the organic anion-transporting polypeptide 1B1 (OATP1B1, gene *SLC01B1*), and also is a substrate of the breast cancer resistance protein (BCRP, gene *ABCG2*), which is an efflux transporter expressed in various normal tissues.
- Genetic polymorphisms of OATP1B1 and BCRP are known to be associated with inter-individual variability in the pharmacokinetics (PKs)/pharmacodynamics (PDs) of rosuvastatin.
- However, there is currently limited information regarding how genetic polymorphisms of OATP1B1 and BCRP quantitatively affect the PK/PD of rosuvastatin using a population approach in young and especially in elderly subjects.

OBJECTIVE

- This study was conducted to determine how genetic polymorphisms of OATP1B1 and BCRP quantitatively influence the PK/PD after multiple administrations of rosuvastatin, and to investigate clinical covariates in healthy young and elderly subjects.

METHODS

- We obtained the PK/PD data from two separate clinical trials, one of which involved 20 elderly subjects (age 65-85 years), and the other of which involved 34 young subjects (age 20-50 years) (Table 1).
- Both studies were designed as open-label, one-sequence, and multiple oral administration of 20 mg of rosuvastatin for 21 days.
- At first, PK/PD parameters were calculated using a non-compartmental method, and then a population PK/PD model was developed using 468 rosuvastatin concentrations at steady state, and 220 low-density lipoprotein cholesterol (LDL-c) concentrations in 52 subjects.
- The First-Order Conditional Estimation with Interaction estimation method was used with NONMEM (version 7.3).

Table 1. Clinical data of rosuvastatin used in the population PK/PD analysis

BCRP	Young							Elderly						
	NF	IF	LF	NF	IF	LF	Total	NF	IF	LF	NF	IF	LF	Total
OATP1B1	NF	NF	NF	NF	IF	LF		NF	IF	LF	NF	IF	LF	
N	10	7	1	9	4	1	32	7	2	8	2	1	1	20
Age (year)	27.5 ± 5.4	29.6 ± 6.1	26.0	26.6 ± 6.2	23.8 ± 5.4	24.0	27.1 ± 7.5	70.7 ± 4.7	69.5 ± 7.9	71.3 ± 5.2	77.5 ± 2.1	68.0	71.4 ± 4.3	
Sex (M/F)	9/1	6/1	1/0	7/2	3/1	0/1	26/6	7/0	2/0	8/0	2/0	1/0	20/0	
Height (cm)	174.9 ± 7.4	170.4 ± 9.5	169.8	173.0 ± 6.6	168.8 ± 7.0	162.8	172.1 ± 7.5	168.3 ± 4.7	165.1 ± 7.9	162.1 ± 5.2	160.3 ± 0.1	157.7	164.2 ± 5.6	
Body weight (kg)	69.6 ± 9.3	66.1 ± 14.3	65.4	67.1 ± 9.5	62.1 ± 8.2	51.5	66.5 ± 10.3	6.0 ± 71.7	0.2 ± 64.8	6.0 ± 68.5	8.1 ± 63.0	8.1	61.8 ± 68.4	
BMI (kg/m ²)	22.7 ± 1.7	22.6 ± 3.0	22.7	22.3 ± 2.1	21.8 ± 2.1	19.4	22.3 ± 2.1	25.3 ± 1.6	23.9 ± 2.2	23.9 ± 26.1	24.5 ± 3.1	24.9	25.4 ± 1.7	
LDL-C (mg/dL)	110.7 ± 35.9	121.9 ± 33.2	127.0	108.6 ± 28.5	95.5 ± 16.5	82.0	110.6 ± 30.1	144.1 ± 45.0	140.5 ± 0.7	117.3 ± 33.7	104.0 ± 8.5	85.0	126.1 ± 37.1	
TC (mg/dL)	171.3 ± 35.5	177.7 ± 26.3	197.0	164.8 ± 21.9	144.8 ± 9.6	165.0	168.2 ± 28.0	222.7 ± 48.7	213.5 ± 7.9	198.1 ± 31.2	170.0 ± 8.5	152.0	203.2 ± 39.1	
TG (mg/dL)	96.1 ± 26.2	121.3 ± 57.3	103.0	82.1 ± 37.9	66.5 ± 12.2	54.0	92.9 ± 37.9	121.0 ± 65.9	77.0 ± 24.0	118.0 ± 40.2	158.5 ± 111.0	140.0	120.1 ± 57.6	
HDL-C (mg/dL)	52.0 ± 8.2	47.0 ± 10.4	62.0	49.7 ± 9.4	46.5 ± 5.1	69.0	50.4 ± 9.3	54.9 ± 9.4	59.0 ± 8.5	57.9 ± 11.7	46.5 ± 14.8	44.0	55.1 ± 10.6	

Values are presented as mean ± standard deviation or number of subjects. Translatorschlophenol (TP) were categorized by genotypes at rs223142 for ABCG2, normal function (NF), OATP intermediate function (IF), AIA, low function (LF) and rs414000 for SLCO1B1 (IF, NF, TC, IF, CC, LF).

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

Values are presented as mean ± standard deviation or number of subjects. Transporter phenotypes were converted by genotypes at rs2231142 for ABCG2 [C/C, normal function (NF); C/A, intermediate function (IF); A/A, low function (LF)] and at rs4349056 for SLC01B1 [T/T, NF; T/C, IF; C/C, LF]. BMI, body mass index; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol.

- The PK structural models of rosuvastatin were investigated with one, two or three-compartment model with zero, first-order or zero and first-order absorption and linear elimination.
- A physiological indirect response model was incorporated to explain the change of LDL-c levels. PD modeling was performed after fixing all the PK parameters.
- The effects of demographics including class (young or elderly), baseline serum creatinine (BSCr), and the phenotypes of OATP1B1 and BCRP on the PK/PD of rosuvastatin were evaluated.
- Visual predictive checks (VPCs) were used to evaluate the stability and robustness of the final PK/PD model.

RESULTS

- Compared with the young, the area under the concentration-time curve from 0 to the dosing interval at steady-state ($AUC_{\tau,ss}$) increased by 22.7 % ($P>0.05$).
- In the young, the mean $AUC_{\tau,ss}$ were increased 1.47-fold ($P=0.001$) with BCRP intermediate function (IF), and in the elderly, increased 1.35- and 1.59-fold ($P>0.05$) with BCRP IF and low function (LF) group (Figure 1).

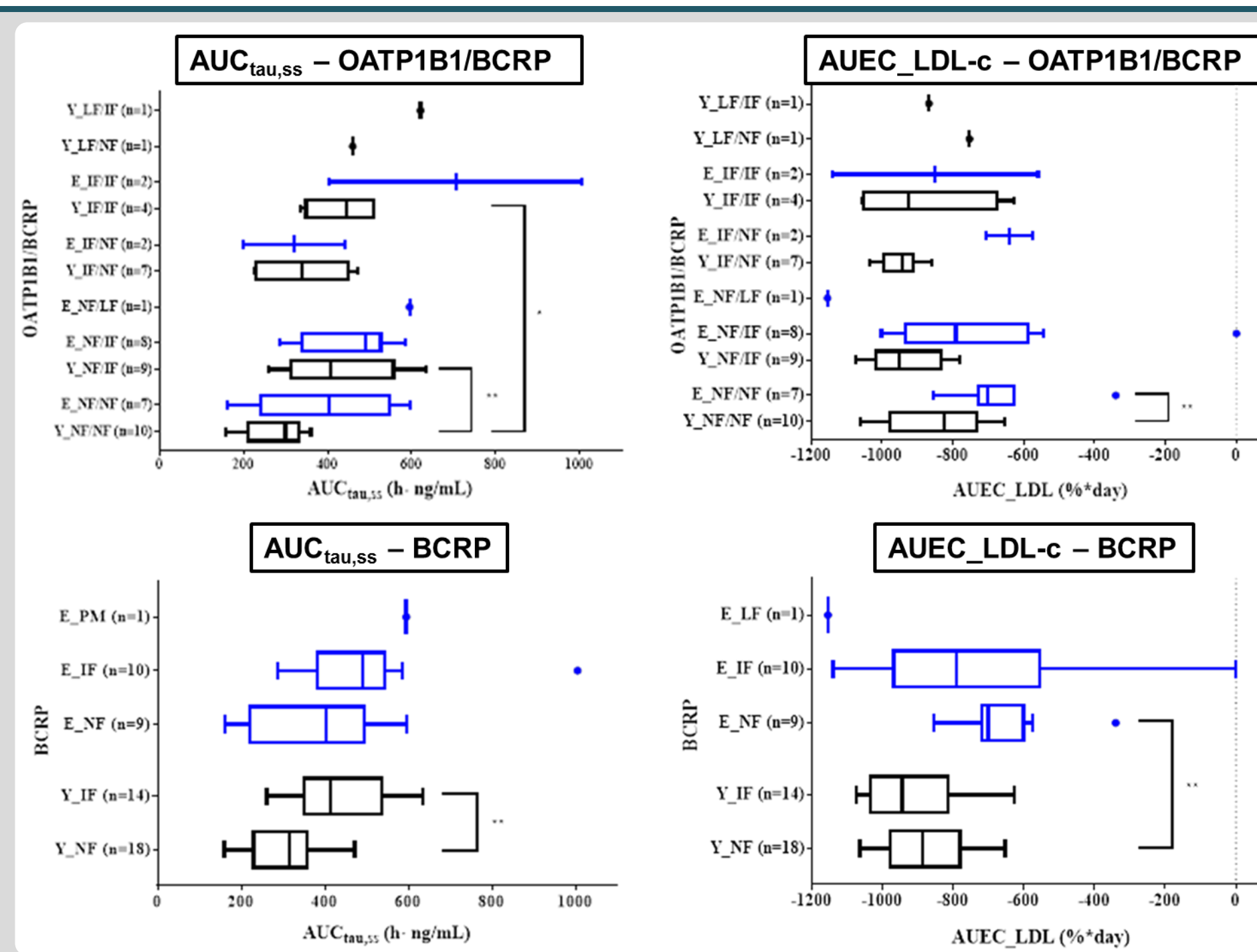


Figure 1. Box-and-whiskers plots of PK/PD parameters ($AUC_{\tau,ss}$, $AUEC_{LDL-c}$) after oral administration of 20 mg rosuvastatin for 21 days according to OATP1B1/BCRP and BCRP phenotypes in young (Y) and elderly (E) subjects. * represents p value < 0.05, ** represents p value < 0.01.

- There was a tendency that lipids lowering effect was less in the elderly when compared to the young, for which the area under the %change from the baseline-time curve of LDL-c ($AUEC_{LDL}$) decreased 0.81-fold ($P=0.0107$) in the elderly.
- In both young and elderly subjects, lipids lowering effect tended to be greater with BCRP variants, but was not statistically significant (Figure 1).
- A two-compartment model with a simultaneous zero- and first-order absorption model along with lag times adequately described the time-concentration profiles of rosuvastatin (Figure 2).
- The profile of the LDL-c lowering effect of rosuvastatin was appropriately described by the physiological indirect response model (Figure 2).

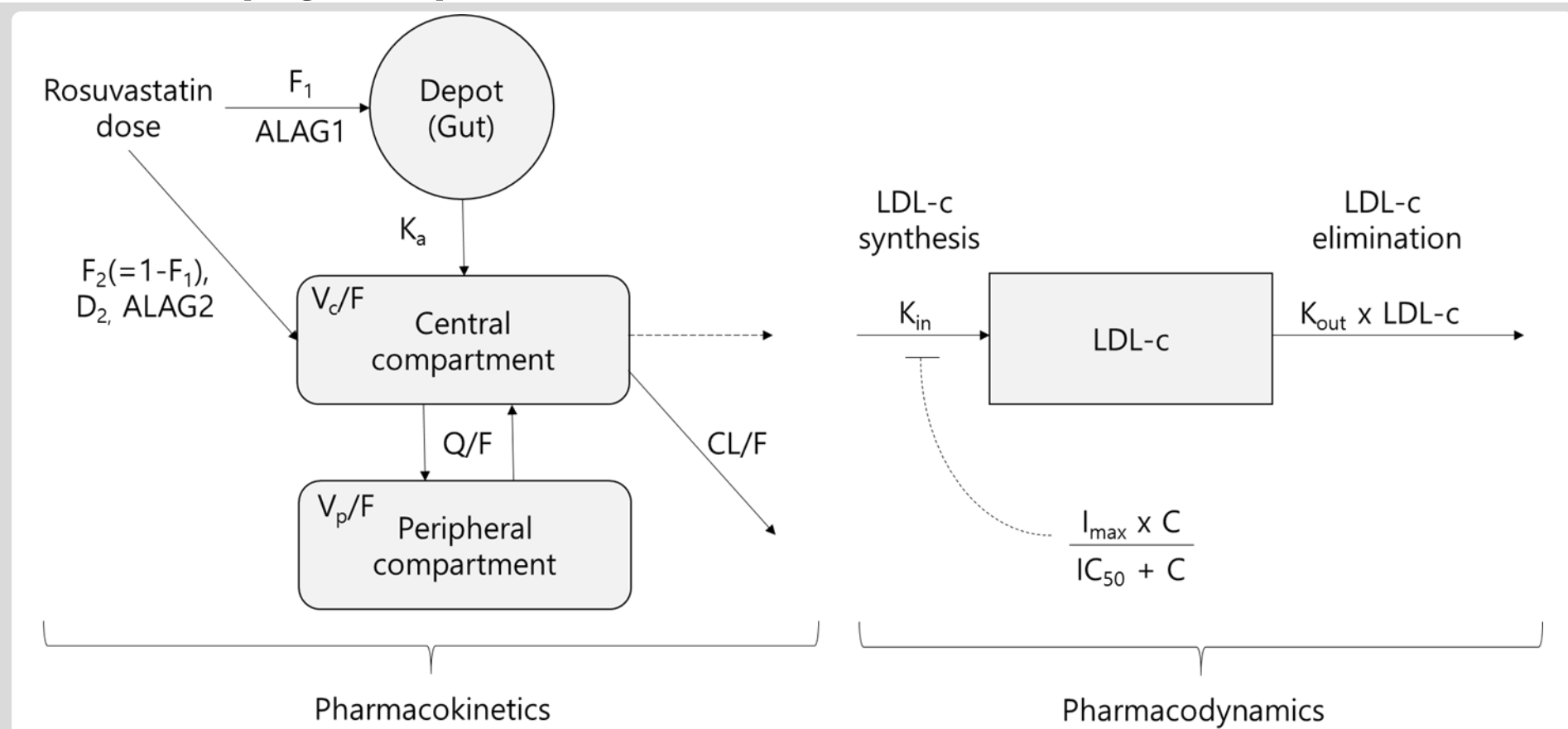


Figure 2. Schematic representation of the final population PK/PD model of rosuvastatin. F_1 , Fraction of bioavailable dose of rosuvastatin for first-order absorption; F_2 , Fraction of bioavailable dose of rosuvastatin for zero-order absorption; D_2 , Duration of zero-order absorption; K_a , Absorption rate constant of first-order absorption; V_c/F , Apparent volume of central compartment; V_p/F , Apparent Volume of peripheral compartment; Q/F , Apparent inter-compartmental clearance; CL/F , Apparent clearance; K_{in} , Zero-order rate constant of LDL-c synthesis; K_{out} , First-order rate constant of LDL-c loss; I_{max} , Maximum value of the inhibitory effect; IC_{50} , Concentration of rosuvastatin resulting in 50% of I_{max} ; C , Concentration of rosuvastatin

- The typical values of the clearance (CL) and inter-compartmental clearance (Q) were found to be 39.7 and 50.9 L/h, respectively (Table 2).
- The absorption process of rosuvastatin was explained by first-order absorption rate constant (k_a , 0.264 /h) with lag time (1.48 h), and duration of zero-order absorption (D_2 , 0.409 h) with lag time (0.675 h).
- The PK model showed that 83.7% of the administered dose of rosuvastatin was absorbed by the first-order process and the remaining 16.3% was absorbed by the zero-order process.
- Reduced function of BCRP, BSCr, and age effect (0: young, 1: elderly) were found to be significant covariates for the CL of rosuvastatin.
- The CL estimates in BCRP IF and LF decreased 24.2% and 50.2% compared to that in NF (Table 2).
- We also observed the CL and Q in elderly were approximately 20% and 16% lower than young subjects, respectively (Table 2).

Table 2. Final parameter estimates of the PK model of rosuvastatin and magnitude of change on PK parameters by significant covariates

Parameters	Description	Estimates	RSE (%)	Magnitude of change (%)
Fixed effect				
CL/F (L/h)	Apparent clearance	39.7	14.5	-
	BCRP IF effect on CL/F	-0.277	38.3	-24.2
	BCRP LF effect on CL/F	-0.697	26.0	-50.2
	Age effect (0: young, 1: elderly) on CL/F	-0.233	44.6	-20.0
	BSCr exponent on CL/F	-1.06	20.4	-
Vc/F (L)	Apparent volume of central compartment	177	15.4	-
Q/F (L/h)	Apparent Inter-compartmental clearance	50.9	10.1	-
	Age effect (0: young, 1: elderly) on Q/F	-0.175	39.5	-16.0
Vp/F (L)	Apparent volume of peripheral compartment	26700	21.3	-
F1	Fraction of bioavailable dose of rosuvastatin for first-order absorption	0.837	2.7	-
D2 (h)	Duration of zero-order absorption	0.409	0.8	-
Ka (1/h)	Absorption rate constant of first-order absorption	0.264	8.9	-
ALAG1 (h)	Absorption lag time for first-order absorption	1.48	2.6	-
ALAG2 (h)	Absorption lag time for zero-order absorption	0.675	0.4	-
Random effect (CV%)				
ω_{CL}	Inter-individual variability of CL	55.4	9.6	-
ω_{Vc}	Inter-individual variability of Vc	57.5	13.5	-
ω_Q	Inter-individual variability of Q	22.6	17.8	-
ρ_{CL-Vc}	Correlation coefficient between CL and Vc	0.26	22.8	-
ρ_{CL-Q}	Correlation coefficient between CL and Q	0.0788	30.1	-
ρ_{Vc-Q}	Correlation coefficient between Vc and Q	0.111	33.2	-
Residual error				
σ_{prop} (%)	Proportional error	19.2	4.3	-

RSE, relative standard error; CV, coefficient of variation; BSCr, baseline serum creatinine level

- Goodness-of-fit plots showed a good adequacy between observed and predicted PK data (Figure 3).

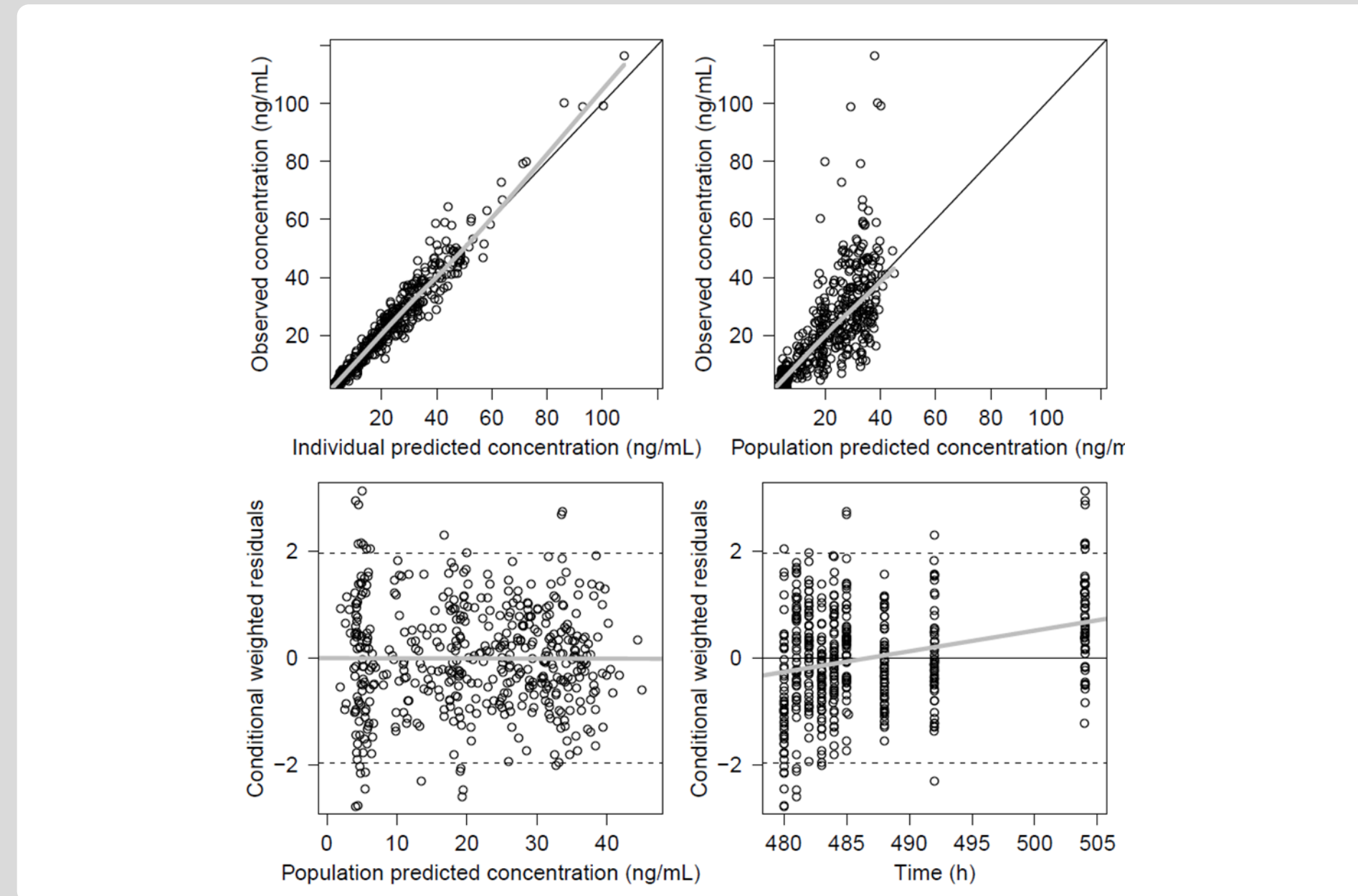


Figure 3. Basic goodness-of-fit plots of the final PK model for rosuvastatin

- Multiple administration of rosuvastatin inhibited the LDL-c synthesis rate constant (K_{in} , 1.26 mg/dL/hr) along with maximum inhibitory effect (I_{max} , 0.917) model and concentration resulting in 50% of I_{max} (IC_{50}) was shown as 0.059 ng/mL (Table 3).
- Baseline of LDL-c was identified with significant covariates (age and body weight) as the following regression equation: Baseline (mg/dL) = $106 \times (Age/29)^{0.147} \times (Body\ weight/67.7)^{0.637}$ (Table 3).
- Compared with the young, IC_{50} and I_{max} values were 28% higher and 6% lower in the elderly, respectively, suggesting the drug potency might be lower in the elderly although this was not statistically significant.

Table 3. Final parameter estimates of the PD model of rosuvastatin

Parameters	Description	Estimates	RSE (%)
Fixed effect			
Baseline (mg/dL)	Baseline level of LDL-c	106	3.9
	Age exponent on baseline	0.147	42.5
	Body weight exponent on baseline	0.637	29.2
K_{in} (mg/dL/hr)	Zero-order rate constant of LDL-c synthesis	1.26	12.9
I_{max}	Maximum value of the inhibitory effect ranging between 0 and 1	0.917	21.4
IC_{50} (ng/mL)	Concentration of rosuvastatin resulting in 50% of I_{max}	0.059	52.9
Random effect (CV%)			
$\omega_{baseline}$	Inter-individual variability of Baseline	19.4	12.6
Residual error			
σ_{add} (mg/dL)	Additive error	5.07	41.6
σ_{prop} (%)	Proportional error	8.11	48.1

RSE, relative standard error; CV, coefficient of variation

- Goodness-of-fit plots showed a good adequacy between observed and predicted PD data (Figure 4).

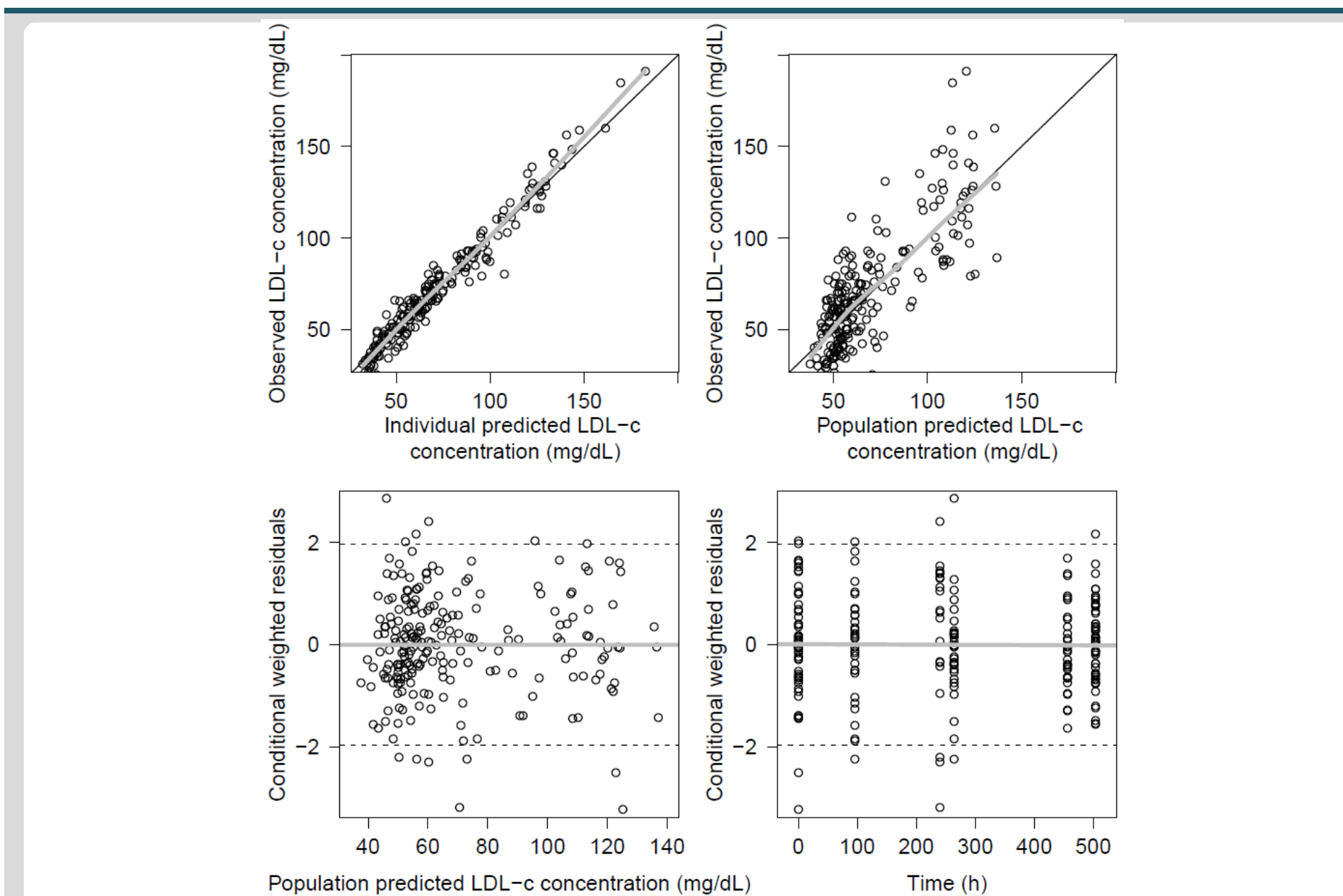


Figure 4. Basic goodness-of-fit plots of the final PD model for rosuvastatin

- Model evaluation by VPCs indicated that the proposed model was adequate and the parameters were estimated with a good precision (Figure 5).

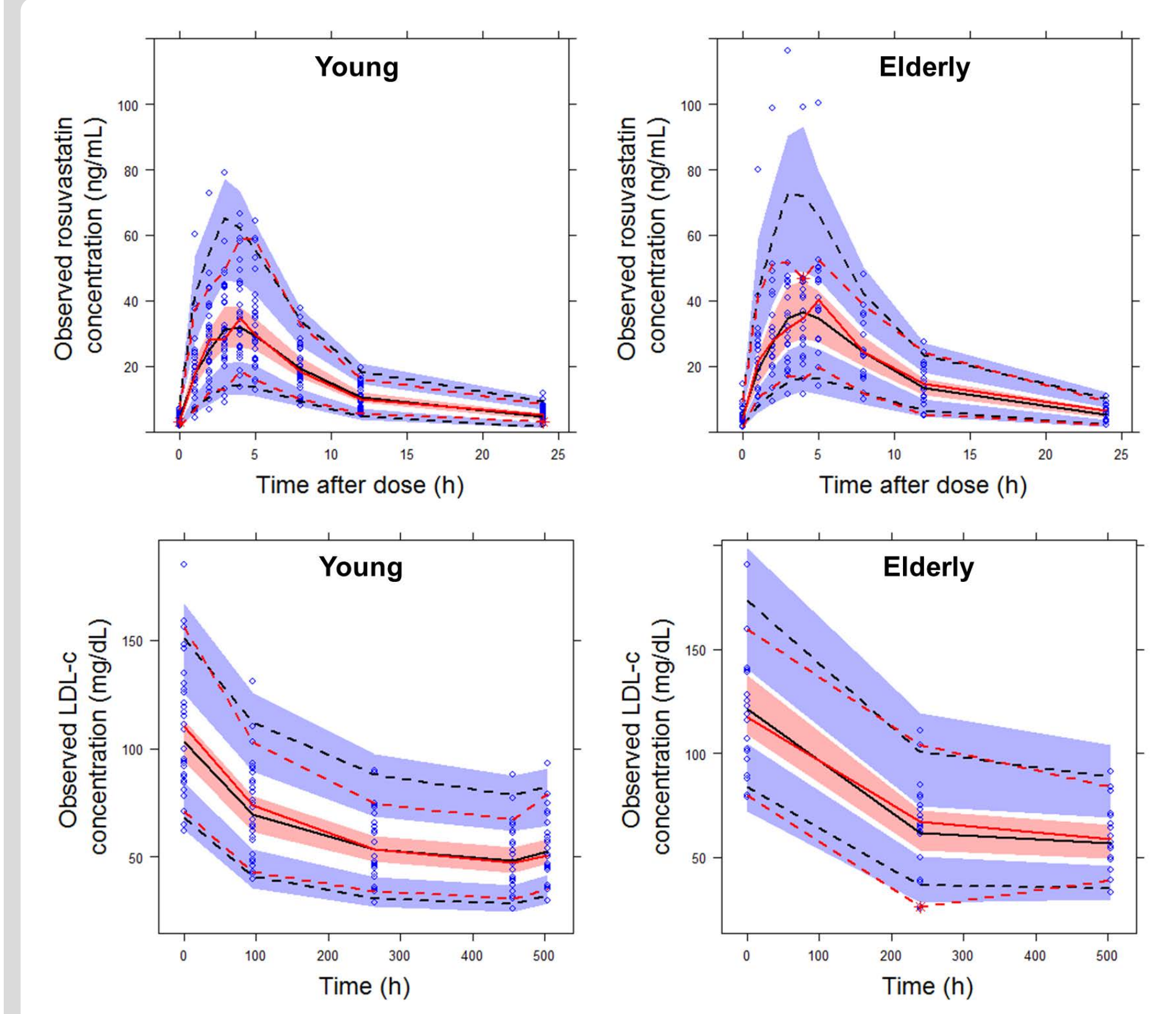


Figure 5. Visual predictive check plots of the final PK/PD model for (a) rosuvastatin and (b) LDL-c according to young and elderly classification. Blue circles represent the observed rosuvastatin concentrations. The red lines represent the median (solid) and the 5th and 95th percentiles (dashed) of the observed concentration. The black lines represents the median (solid) and 5th and 95th percentiles (dashed) of the simulated concentrations. The areas represent the 95% confidence intervals for the median (red) and for the prediction percentiles (blue).

CONCLUSION

- The PK/PD parameters of rosuvastatin were quantitatively described by the developed population model.
- This PK/PD model in the contribution of BCRP, age effect, and demographic data to the variability of rosuvastatin can be served as a tool to predict the PK/PD of rosuvastatin, thus providing a rationale for individualized optimal dosing to improve clinical outcome.

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