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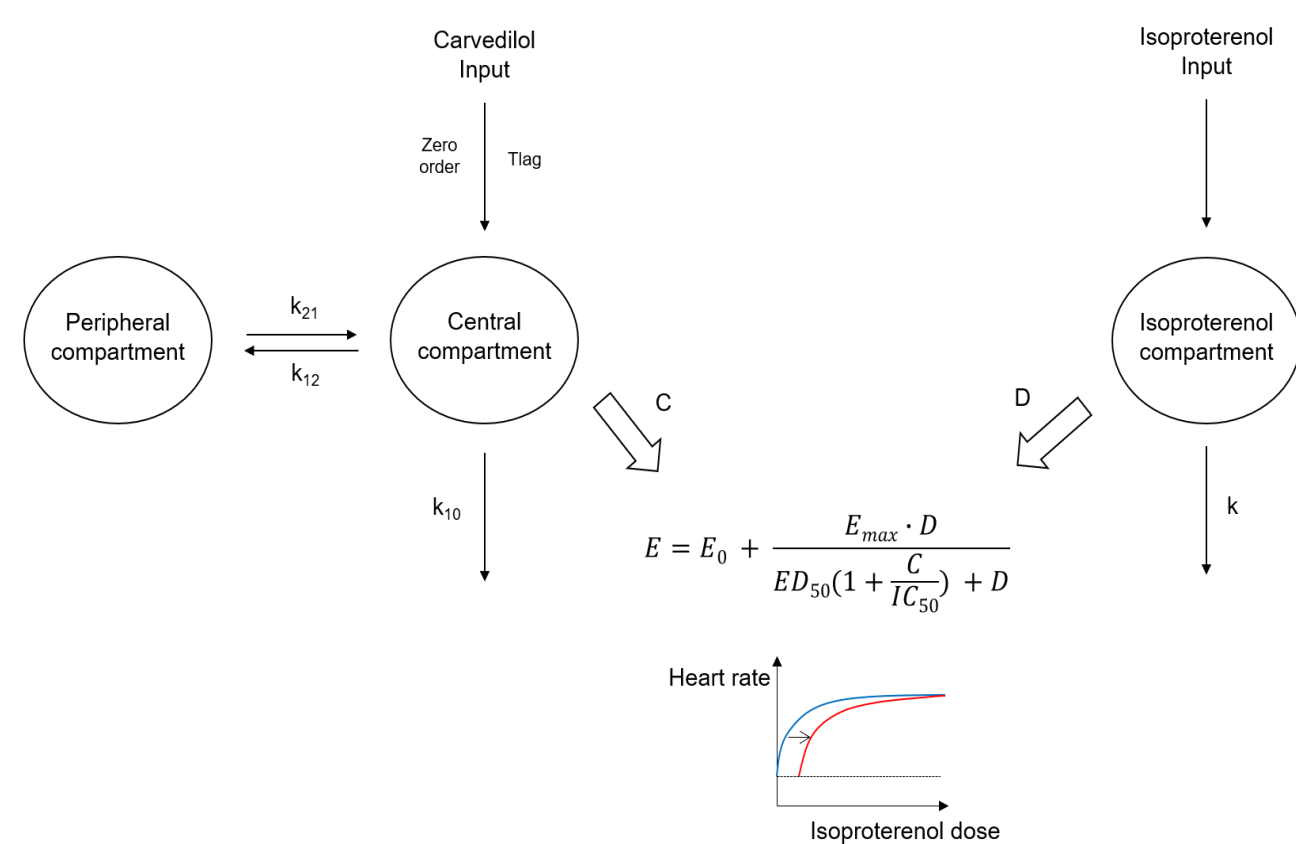
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## OBJECTIVES

- Carvedilol is an adrenergic receptor antagonist and used as first-line therapy for cardiovascular disease including hypertension.
- It is mainly metabolized by cytochrome P450 enzyme (CYP) 2D6 and CYP2C9 and the active metabolites are less than 10% of the parent form.
- The study aimed to establish the population pharmacokinetic (PK) - pharmacodynamic (PD) model of carvedilol and explored the impact of CYP2D6 genetic polymorphism on PK and PD properties of carvedilol.

## METHODS

- The PK-PD model was developed from a clinical study conducted in healthy subjects with three CYP2D6 phenotype groups.
- Of 21 subjects, six subjects were CYP2D6 extensive metabolizer (EM, \*1/\*1, \*1/\*2), seven subjects were intermediate metabolizer-1 (IM-1, \*1/\*10, \*2/\*10), and eight subjects were intermediate metabolizer-2 (IM-2, \*10/\*10).
- All subjects received oral doses of carvedilol 12.5 mg QD (3 days), sequentially 25 mg QD (5 days), and 12.5 mg (3 days).
- Isoproterenol sensitivity test was conducted to measure the effect of carvedilol suppressing tachycardia induced by isoproterenol.
- The PK-PD model was developed sequentially using nonlinear mixed-effect modeling (NONMEM) software (version 7.4).
- A total of 450 plasma observations and 1003 heart rate observations were used for the construction of the PK and PD model, respectively.
- The changes in heart rates induced by isoproterenol were explored using a simple  $E_{max}$  or sigmoid  $E_{max}$  model.
- The PD model was linked with PK by computing individual PK parameters of the final PK model. A direct effect response and inhibitory  $E_{max}$  model was used for developing the PK-PD model of carvedilol.
- The final model was evaluated by assessing goodness-of-fit (GOF) plots, visual prediction checks (VPC), and bootstrapping.



C, concentration of carvedilol; D, dose of isoproterenol;  $ED_{50}$ , half maximal effective dose of isoproterenol;  $E_{max}$ , maximal effect of isoproterenol;  $IC_{50}$ , Half maximal inhibitory concentration of carvedilol; k, elimination rate constant of isoproterenol;  $k_{10}$ , elimination rate constant of carvedilol from the central compartment;  $k_{12}$ , rate transfer constant from the central to peripheral compartment;  $k_{21}$ , rate transfer constant from the peripheral to central compartment; Tlag, lag time for zero-order absorption

$$E = E_0 + \frac{E_{max} \cdot D}{ED_{50}(1 + \frac{C}{IC_{50}}) + D}$$

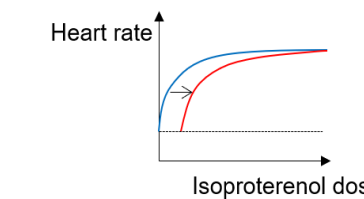


Figure 1. Final pharmacokinetics (PK) and pharmacodynamics (PD) model structure of carvedilol. The PD model was developed based on the changes in heart rate from the isoproterenol sensitivity test. The final PK/PD model describes the PK of carvedilol and changes of heart rate in response to carvedilol.

Table 1. Parameter estimation of final PK model, and bootstrap results for carvedilol

	Final model <sup>a</sup>	Bootstrap (n = 1000)
	Estimate (RSE, %)	Median (95% CI)
<b>Population parameters</b>		
D1 (h)	0.383 (70)	0.390 (0.330 – 0.515)
Tlag (h)	0.215 (0.6)	0.205 (0.166 – 0.246)
CL (L/h) <sup>b</sup>	153 (0.7)	147.6 (131 – 170)
IM-2 effect on CL	0.328 (14.6)	0.314 (0.203 – 0.417)
V1 (L)	440 (35)	414 (365 – 501)
V2 (L)	754 (2.3)	732 (553 – 992)
Q (L/h)	41.3 (5.1)	41.3 (35.6 – 50.9)
<b>Interindividual variability (coefficient of variation, CV%)</b>		
$\omega_{Tlag}$	56.8 (12.9)	57.7 (33.9 – 108.5)
$\omega_{CL}$ (%)	14.6 (9.8)	12.9 (7.8 – 17.9)
$\omega_{V1}$ (%)	26.1 (9.2)	17.2 (2.4 – 31.1)
<b>Residual error</b>		
Proportional error	0.379 (2.2)	0.376 (0.339 – 0.404)

<sup>a</sup> 2-compartment with zero-order absorption with a lag time with the covariate of effect of CYP2D6 genotype on clearance

<sup>b</sup>  $CL (L/h) = 153 \cdot (1 - 0.328 \cdot GT)$ ;  $GT = 1$  (CYP2D6 \*10/\*10 allele) or 0 (CYP2D6 \*1/\*1, \*1/\*2 or CYP2D6 \*1/\*10, \*2/\*10)

RSE (%) = (Standard error) / (Estimate) x 100

Abbreviations: D1, duration of zero-order absorption; CI, confidence interval; CL, clearance; IM-2, intermediate metabolizer (CYP2D6\*10/\*10); Q, inter-compartmental clearance between central and peripheral compartment; Tlag, absorption lag time; V1, volume of distribution of central compartment; V2, volume of distribution of peripheral compartment

Table 2. Parameter estimation of final PK model, and bootstrap results for carvedilol

	Final model <sup>a</sup>	Bootstrap (n = 1000)
	Estimate (RSE, %)	Median (95% CI)
<b>Population parameters</b>		
$E_0$	60.4 (3.1)	60.4 (56.9 – 64.0)
$ED_{50}$	0.685 (30.9)	0.709 (0.387 – 1.512)
$E_{max}$	30.7 (21.9)	31.7 (20.2 – 52.1)
$IC_{50}$	16.5 (34.4)	16.6 (9.3 – 39.4)
<b>Interindividual variability (coefficient of variation, CV%)</b>		
$\omega_{E_0}$ (%)	13.5 (12.7)	13.2 (9.2 – 16.1)
$\omega_{E_{max}}$ (%)	65.4 (27)	57.6 (31.7 – 109.0)
<b>Residual error</b>		
Additive error	64.2 (5.9)	63.1 (50.6 – 79.1)

<sup>a</sup> Effect =  $E_0 + (E_{max} \cdot \text{Dose}) / [ED_{50}(1 + \text{Concentration}/IC_{50}) + \text{Dose}]$

RSE (%) = (Standard error) / (Estimate) x 100

Abbreviations:  $E_0$ , baseline heart rate;  $ED_{50}$ , half maximal effective dose of isoproterenol;  $E_{max}$ , maximal effect of carvedilol;  $IC_{50}$ , inhibitory potency of carvedilol

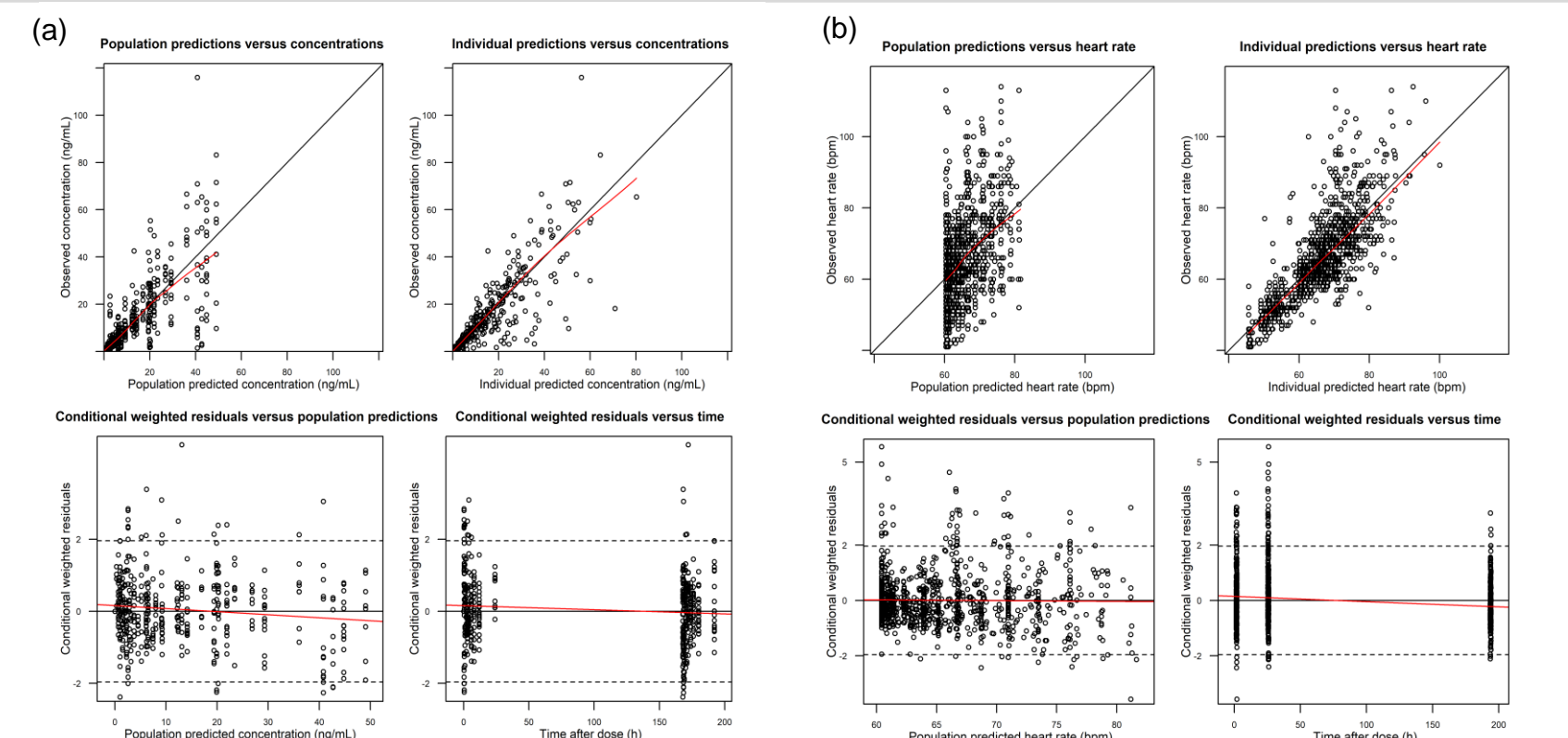


Figure 1. Goodness-of-fit plots of carvedilol of (a) the final PK model and (b) final PK-PD model. Open circles indicate observations; solid black lines are the lines of identity; red lines are the line of locally weighted scatterplot smoothing.

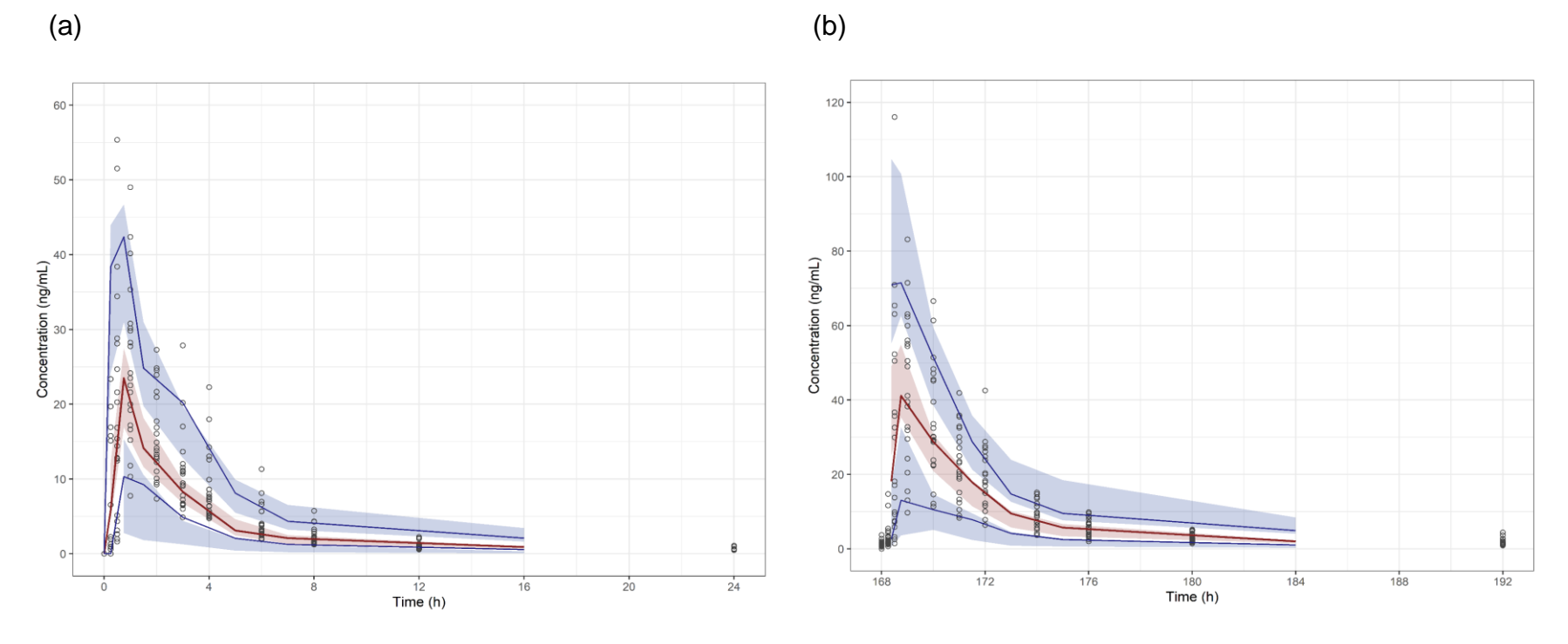


Figure 2. Visual Predictive Checks (VPC) of the final PK model after (a) a single dose of carvedilol 12.5 mg and (b) multiple doses of carvedilol 25 mg. The open circles represent the observed carvedilol plasma concentrations; the solid lines represent the 5th (blue), median (red), and 95th (blue) percentiles of the observed concentration; the blue and red areas indicate the 95% confidence interval of the simulated concentrations of each percentile.

## RESULTS

- The PK of carvedilol was well described by a two-compartment model with zero-order absorption, and absorption lag time, and first-order elimination (Figure 1).
- The population PK parameter estimates (relative standard error, RSE) of clearance (CL) in EM and IM-1, the volume of distribution of central compartment (V1) and peripheral compartment (V2) were 153 L/h (0.7%), 440 L (35%), and 754 L (2.3%), respectively (Table 1).
- The estimates (RSE) of duration of zero-order absorption (D1), absorption lag time (Tlag), and inter-compartmental clearance (Q) were 0.38 h (70%), 0.22 h (0.6%), and 41.3 L/h (5.1%), respectively (Table 1).
- The clearance of carvedilol decreased 32.8% in the CYP2D6\*10/\*10 group compared to the other groups (Table 1).
- The population PD parameter estimates (residual standard error) of baseline heart rate ( $E_0$ ), the potency of isoproterenol ( $ED_{50}$ ), and maximal effect of carvedilol ( $E_{max}$ ) on heart rate reduction were 60.4 bpm (3.1%), 0.69  $\mu$ g (30.9%), and 30.7 bpm (21.9%), respectively (Table 2).
- The  $IC_{50}$  estimated from the final PK-PD model was 16.5 ng/mL regardless of the CYP2D6 phenotype (Table 2).
- The model evaluation by GOF plot, VPC, and bootstrapping results suggested that the final PK-PD model was robust and adequate with good precision (Figure 2, 3).

## CONCLUSION

- The PK-PD model identified that the decreased function allele of CYP2D6 affected the clearance of carvedilol and the genotype effect on the PD appears to be minimal.

## REFERENCES

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