Supplemental Data

Journal Title

Drug Metabolism and Disposition

Article Title

Predicting stereo-selective disposition of carvedilol in adult and pediatric chronic heart failure patients by incorporating pathophysiological changes in organ blood flows–A physiologically based pharmacokinetic approach

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Supplemental Methods

Sensitivity Analysis

In order to assess the uncertainty associated with some pediatric model input parameters, which were adopted from adult PBPK model, sensitivity analysis (SA) was performed. The SA was performed on parameters that have the highest potential effect on the clearance (as oral clearance *CL/F*) and area under the curve ($AUC_{0-\infty}$) of both enantiomers, i.e., hepatic (portal and arterial), P_{eff} and $f_{u,Gut}$.

Sensitivity index (SI) was used to determine the magnitude of change in output of the parameter (PK-parameters) per unit change in the magnitude of input parameter from its initial value.

The SI is determined by using the following relation **(Supplemental equation 1)** implemented within Simcyp® version 14.1,

$$SI_n = \left(Q(P_{n+1}) - Q(P_n)\right) \Big/ (P_{n+1} - P_n) \qquad (1)$$

Where SI is the sensitive index for the output variable which is function of parameter *Q(P)* with respect to change in the value of input parameter *P* from the initial value P_n.

The SA showed that the predicted *CL/F* and $AUC_{0-\infty}$ in pediatric CHF patients were most sensitive to changes in $f_{u,Gut}$, hepatic portal blood flow, and P_{eff} **(Supplemental Figure 1).** However, the PK parameters of interest were only sensitive to P_{eff} at low values, which is not expected in the case of carvedilol as it is a BCS II drug with high permeability and a P_{eff} value of <1 is not reasonable, which leaves the $f_{u,Gut}$ and hepatic portal blood flow as the most sensitive parameters. This finding was further confirmed from the simulated plasma concentration-time profiles of R and S-carvedilol after periodically changing the values of input parameters in 10 consecutive runs **(Supplemental Figure 2).**

Due to the lack of measured/reported data for these parameters, it was not plausible to use different values of input parameters in adult and pediatric CHF populations. Therefore, as mentioned previously in

the modelling strategy, the evaluated adult CHF model was scaled to pediatric CHF patients by keeping all the input parameters consistent with the evaluated adult PBPK model.

Supplemental Table 1 Comparison of area under the systemic drug concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and area under the systemic drug concentration-time curve from time zero to last measured concentration (AUC_{last})

Population	R-Carvedilol		S-Carvedilol		Reference
	$Ratio_{(observed/predicted)}$				
	AUC_{last}	$AUC_{0-\infty}$	AUC_{last}	$AUC_{0-\infty}$	
Adults					
Healthy adults (iv)	1.00	1.06	0.99	1.06	(Neugebauer et al., 1990);
Healthy adults (50 mg oral)	0.93	0.99	0.88	0.99	(Spahn et al., 1990)
Healthy adults (0.09 mg/kg oral)	0.99	1.04	0.76	0.92	(Behn, 2001)
Healthy adults (EM)	1.47	1.44	1.52	1.66	(Zhou and Wood, 1995)
Healthy adults (PM)	1.12	1.09	1.00	1.05	
Adults with CHF	1.18	1.23	0.94	1.11	(Tenero et al., 2000)
Pediatrics					
All patients	0.84	0.83	0.83	1.00	(Behn, 2001)
Infants	0.71	0.84	0.62	0.74	
Young children	1.21	1.24	1.63	1.72	
Children	1.08	1.10	0.91	1.11	
17.8 year	0.89	0.93	0.93	1.28	
17.5 year	2.65	2.73	2.25	2.50	
17.5 year[a]	1.63	1.49	1.08	1.04	
19.3 year	1.84	1.67	2.52	3.01	
19.3 year[a]	0.74	0.57	0.67	0.68	

[a] predictions with organ blood flow reductions, *iv*: intravenous, *EM*: extensive metabolizers, *PM*: poor metabolizers and *CHF*: chronic heart failure

Figure Legends

Supplemental Figure 1 Sensitivity analysis on various model input parameters and their effect on predicted oral clearance (CL/F) and area under the curve ($AUC_{0-\infty}$) of R and S carvedilol in pediatric chronic heart failure patients. *Liver hepatic blood flow* (% of cardiac output) (A, B, C, D), *liver arterial blood flow* (% of cardiac output) (E, F, G, H), *human jejunum permeability* (P_{eff}) (I, J, K, L) and *fraction of unbound drug in gut* ($f_{u,Gut}$) (M, N, O, P). Y-axis on the right side shows sensitivity index and on the left side shows *CL/F* and $AUC_{0-\infty}$. Solid lines indicate *CL/F* and $AUC_{0-\infty}$. The dotted line indicates sensitivity index. The solid circles (●) show the value of the parameter used in healthy male population. The grey shaded area shows the range of reduced organ blood flow used for performing simulations in chronic heart failure patients.

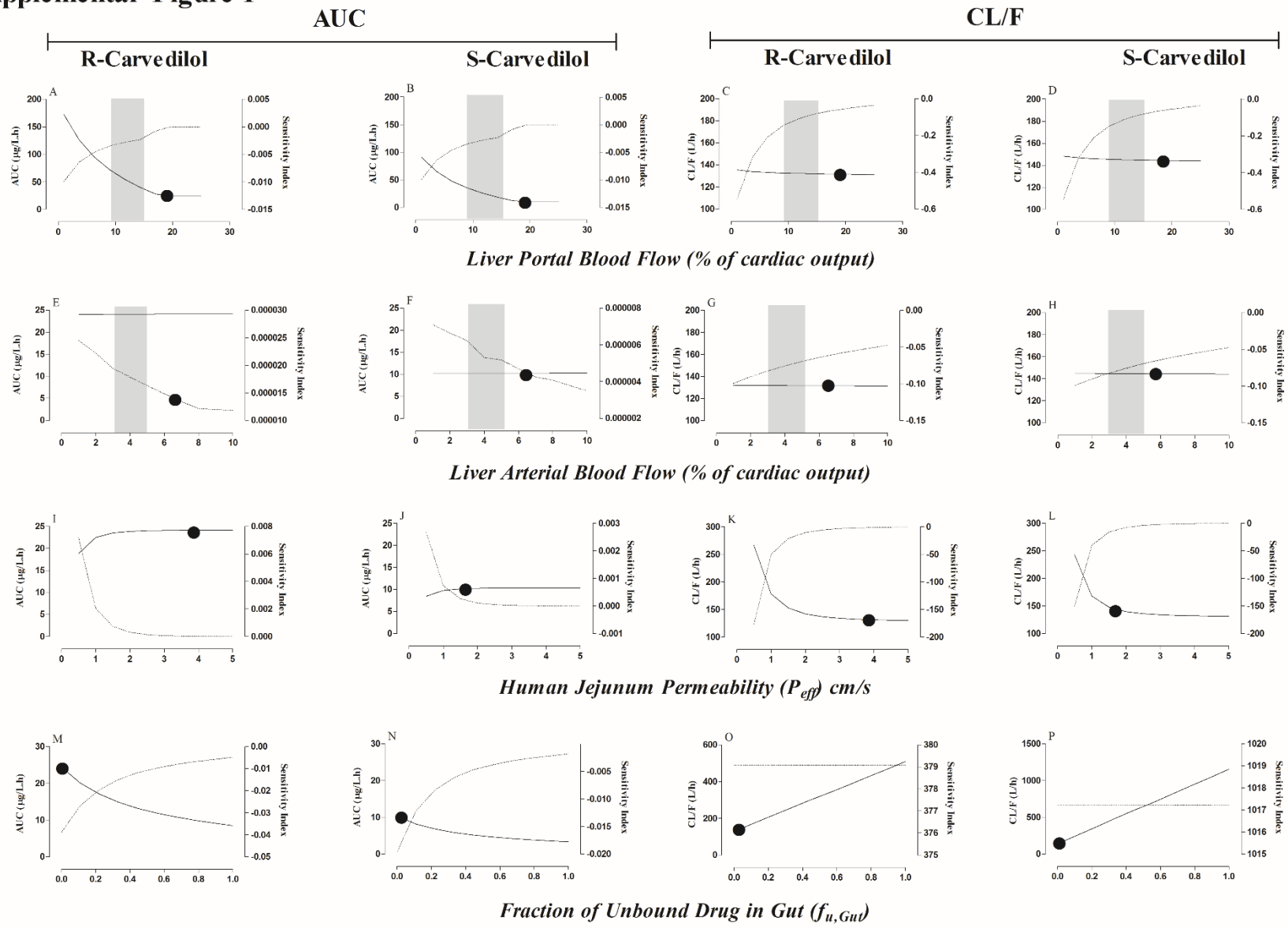
Supplemental Figure 2 Predicted R and S-carvedilol systemic concentration vs. time profiles from the sensitivity analysis by changing the values of input parameters in 10 runs. *Liver hepatic blood flow* (% of cardiac output), simulated range: 1–25 % (A, B), *liver arterial blood flow* (% of cardiac output), simulated range: 1–10 % (C, D), *human jejunum permeability* (P_{eff}), simulated range: 0.5–5 cm/s (E, F) and *fraction of unbound drug in gut* ($f_{u,Gut}$), simulated range: 0–1 (G, H).

Supplemental Figure 3 Observed vs. predicted concentrations plots in healthy adults after intravenous (A, B), and oral (C, D) racemic carvedilol application, and in chronic heart failure patients after oral application racemic carvedilol (E, F). The solid line indicates line of identity and the dashed line show a 2-fold error range.

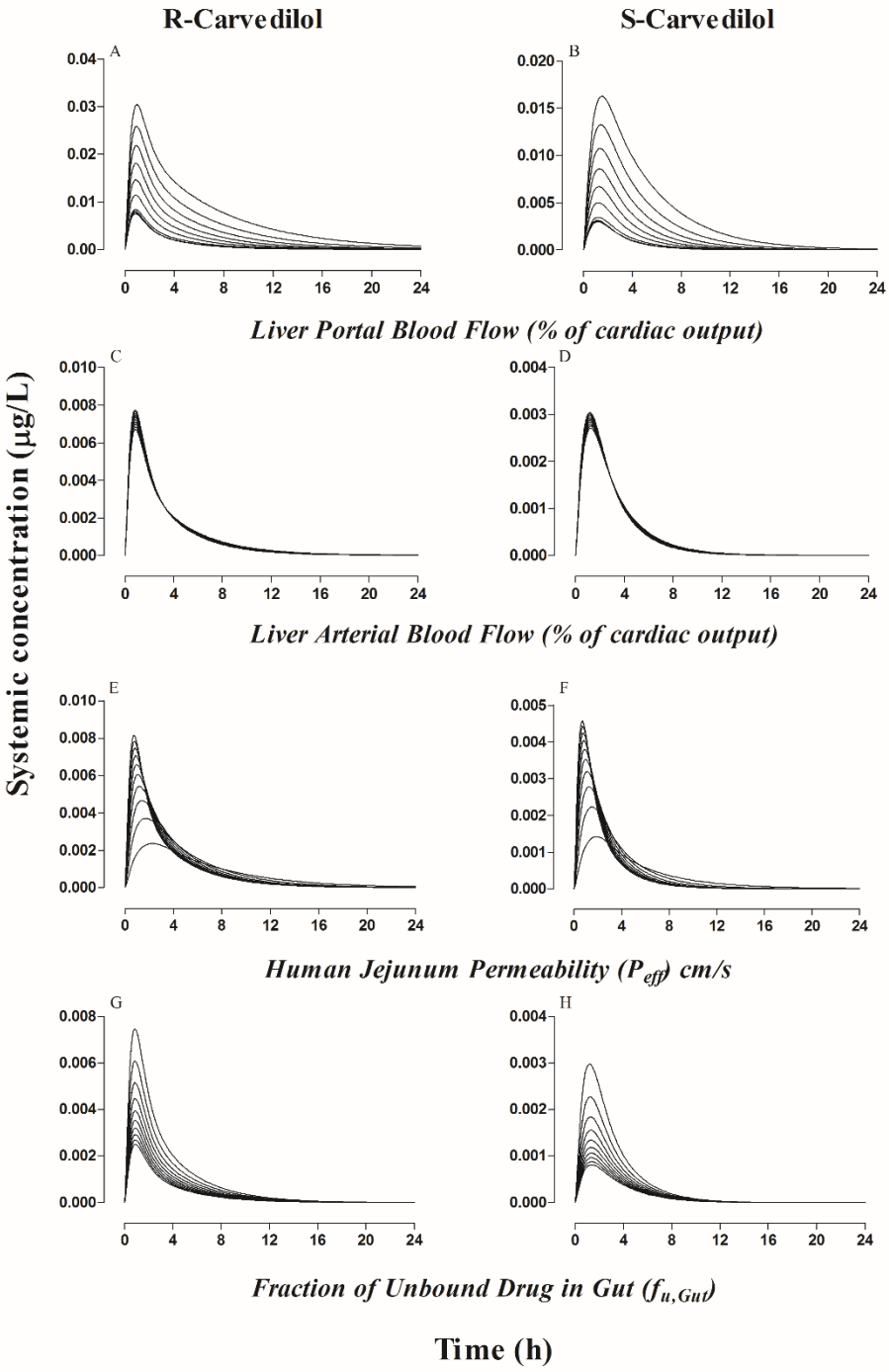
Supplemental Figure 4 Model predictions in the entire pediatric age range n=15 (0.12 to 17.8 year) including the young adult n=1 (19.3 year) after administering 0.09 mg/kg racemic carvedilol, (A, B) systemic concentration-time plots, ○ observed data — median prediction, ---- minimum and maximum prediction, ···· 5^{th} and 95^{th} percentiles and (C, D) Change in oral clearance of R and S-carvedilol with age ○ Predicted CL/F, ● observed CL/F (Behn, 2001). Simulations performed by creating a virtual population of 1000 individuals.

Supplemental Figure 5 Observed vs. predicted concentrations plots in pediatric CHF patients after administering 0.09 mg/kg racemic carvedilol (a, b). The solid line indicates line of identity and the dashed line show a 2-fold error range.

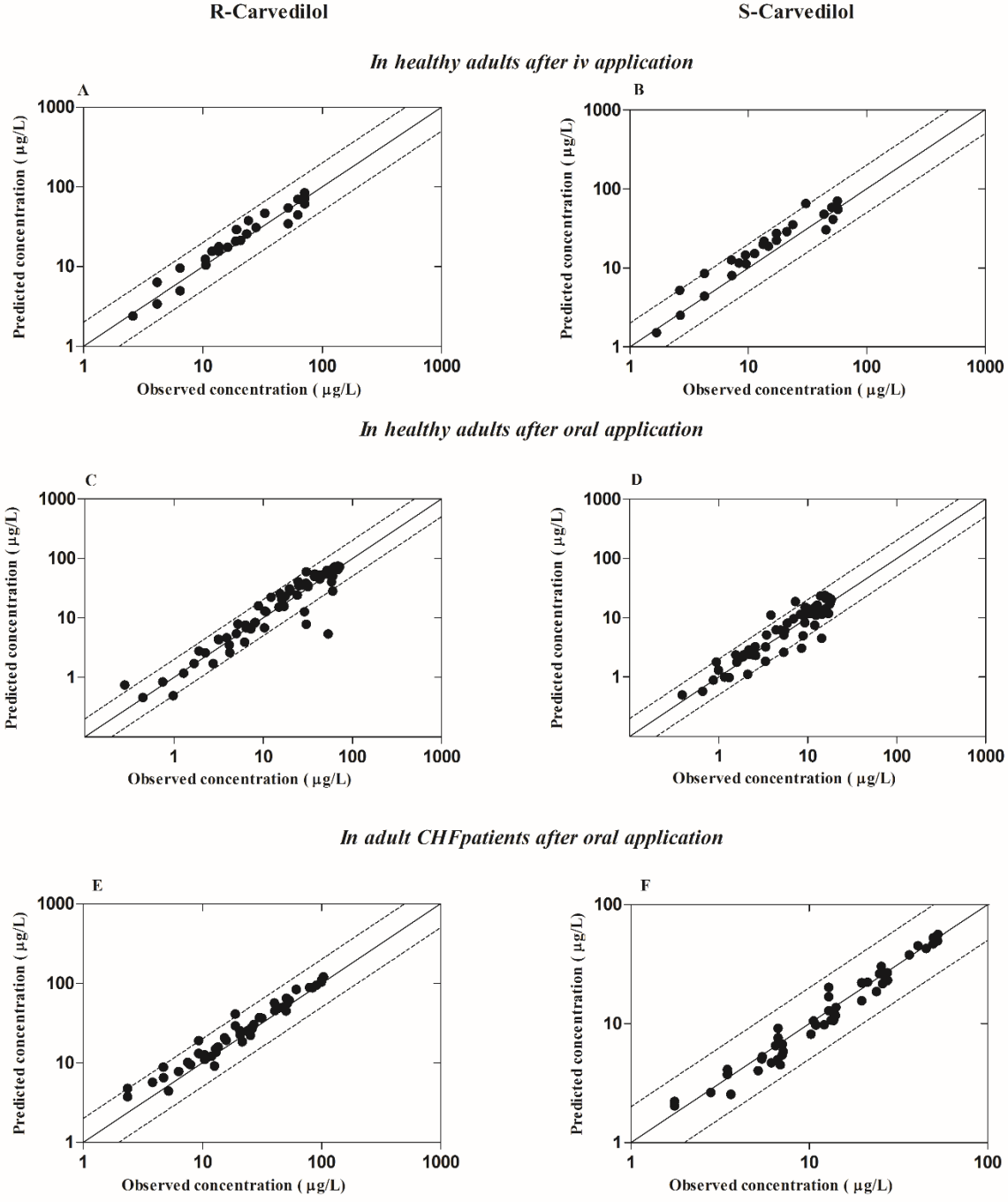
Supplemental Figure 1



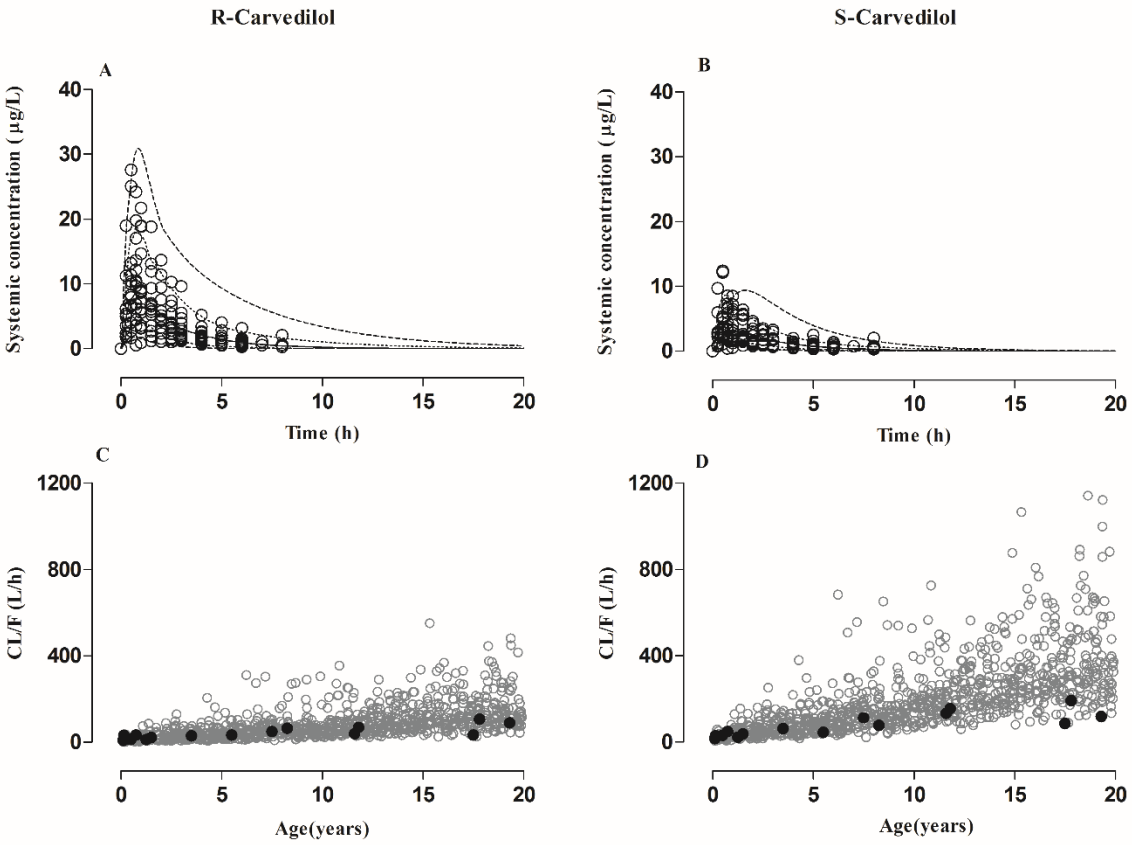
Supplemental Figure 2



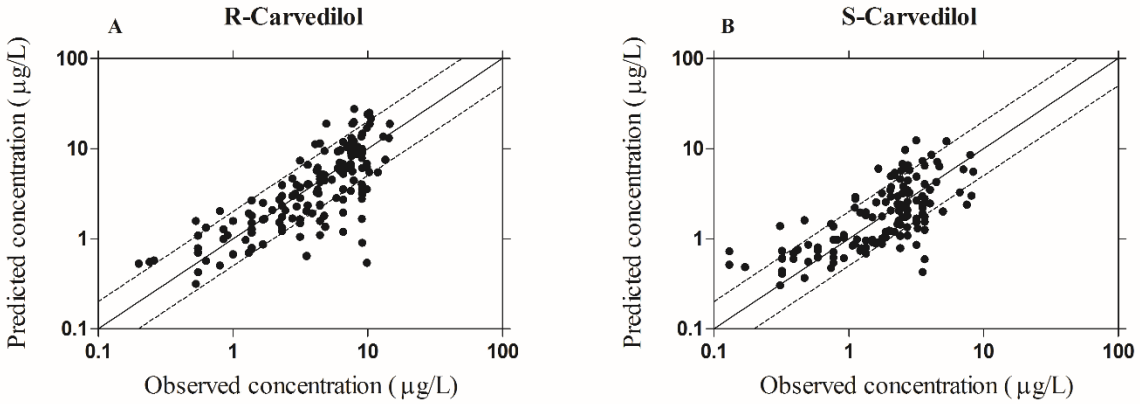
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



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