Supplement 2:

Abstraction and extraction of intravenous data from the publication by Neugebauer et al., 1990.

A meta-analytical approach was considered along with the implementation of the data analysis using Bayesian priors on the parameters of interest. Given the somewhat complex model structure that is required for the characterisation of the individual enantiomers, a decision was made to combine simulated data after intravenous administration with the clinical trial data after oral administration of carvedilol.

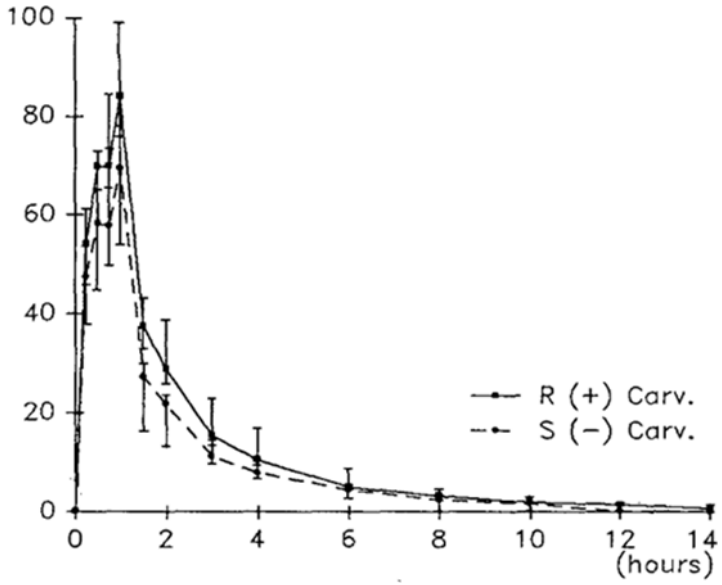
First, a population pharmacokinetic model was implemented in NONMEM v.7.2 (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation mode with interaction (FOCE-I). The pharmacokinetic model was developed using the ADVAN6 subroutine with a GNU Fortran 4.6 compiler (Free Software Foundation, Inc.) and PsN (*Perl-speaks*-NONMEM, Uppsala University, Sweden), version 3.5.3. R, v. 3.1.2 (R Development Group, Vienna) was used for data manipulation, graphical and statistical summaries.

Model building criteria included a decrease in the objective function value (OFV), a successful minimisation, adequate standard error of estimates and number of significant digits, and evaluation of parameter correlation. Fixed and random effects were introduced in a stepwise manner.

Carvedilol concentration vs. time profiles were best described by a two-compartment structural model with first order absorption and elimination (figure S2). As individual data were not available, inter-individual variability could not be estimated. It was imputed at a later step based on the reported standard deviations (table S2). Figure S3 presents the model fitting to the observed data of the original publication by Neugebauer et al. (1990) Model diagnostics indicated adequate goodness-of-fit for the final model, in that the estimated parameter distributions accurately described the original data and its variability (figure S4).

Finally, 13 simulated profiles were generated corresponing to different percentiles of the parameter distributions (0.025, 0.05, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 0.95, 0.975) (figure S5). These profiles were merged with the data of carvedilol enantiomers after oral administration.

A



B

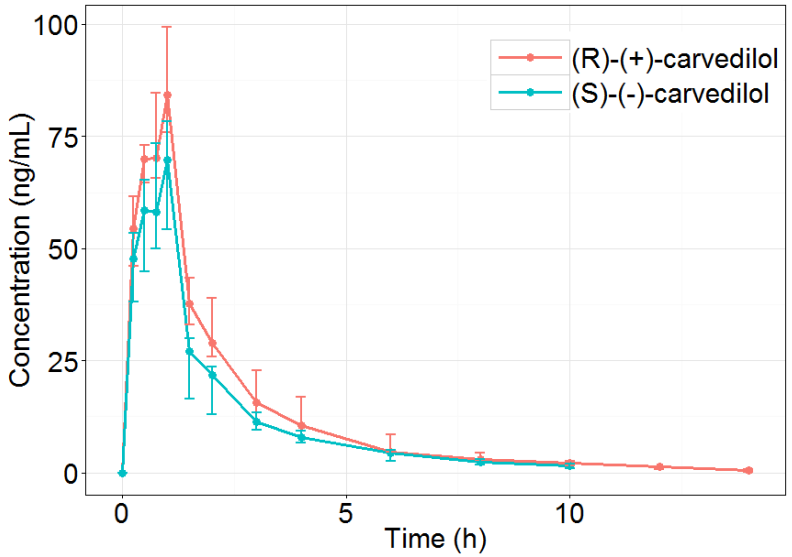


Figure S1: Median plasma concentration vs. time profiles of (R)-(+) and (S)-(-)-carvedilol reported by Neugebauer et al (1990) along with the observed quartiles (A), and the corresponding digitised data (B).

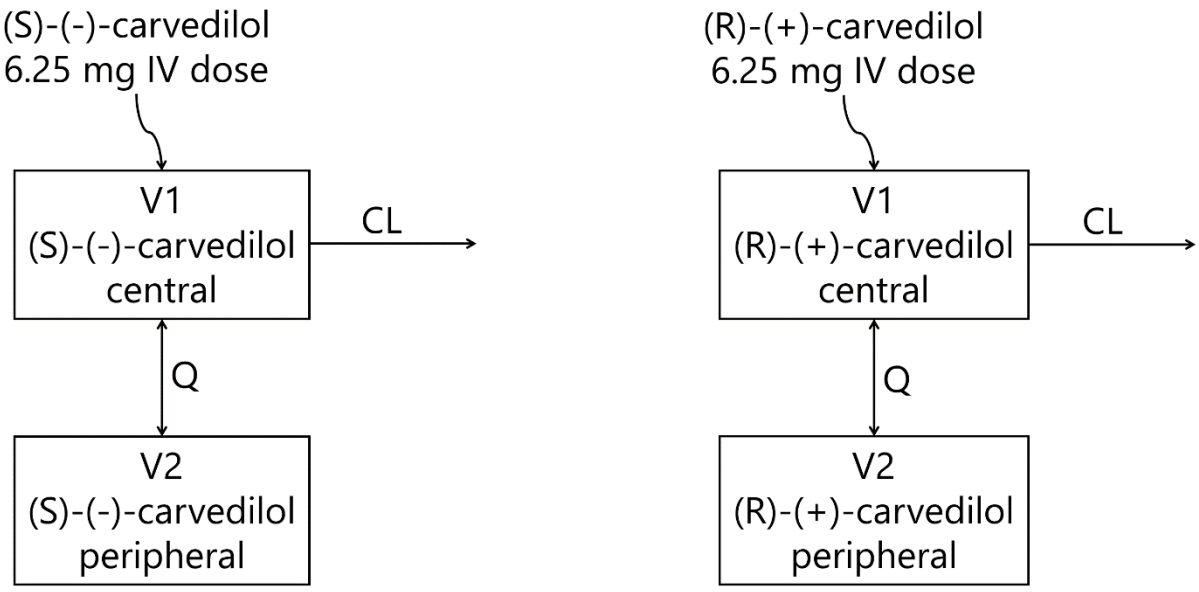


Figure S2: Two-compartment model describing the pharmacokinetics of carvedilol enantiomers following a 1 h infusion of 12.5 mg racemic carvedilol.

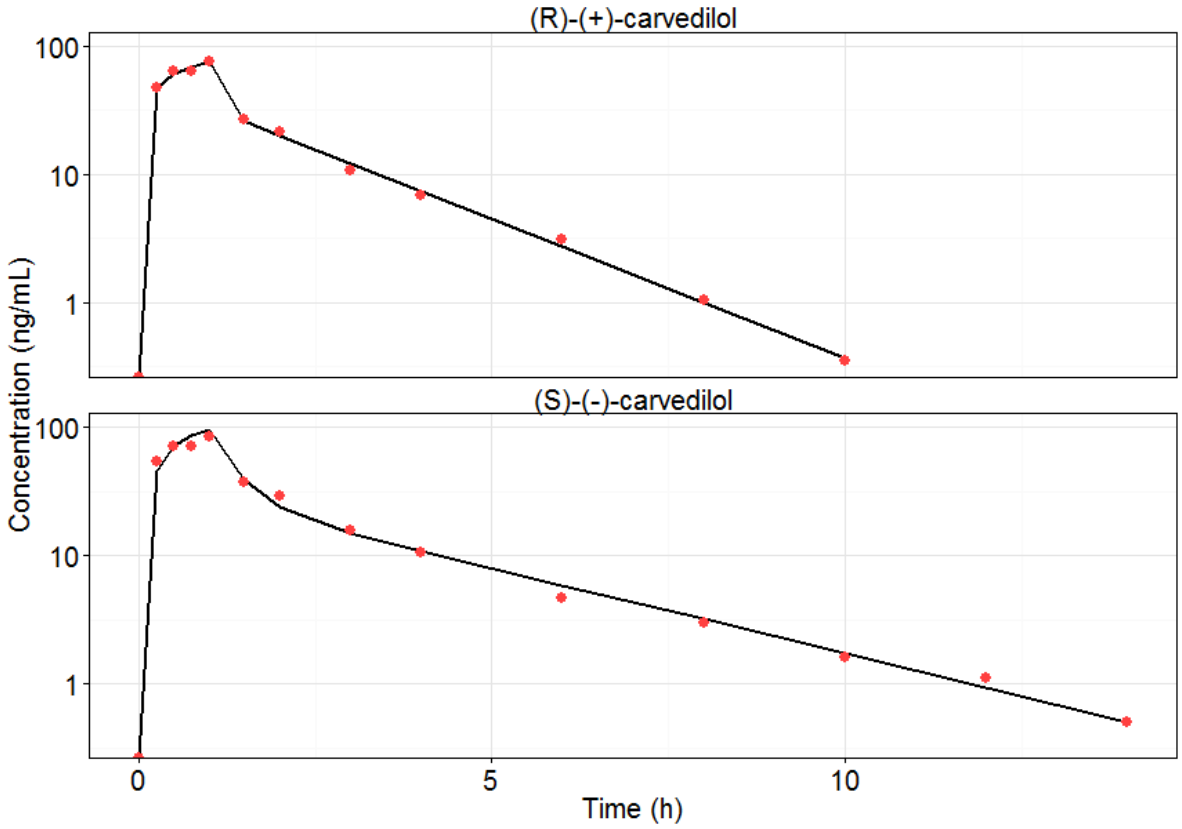


Figure S3: Goodness of fit plots (GOF) of the carvedilol plasma concentration vs. time following a 1 h infusion of 12.5 mg racemic carvedilol. **Solid line**: Predicted plasma concentration. **Dots**: Median of observed plasma concentrations reported by Neugebauer et al. (1990).

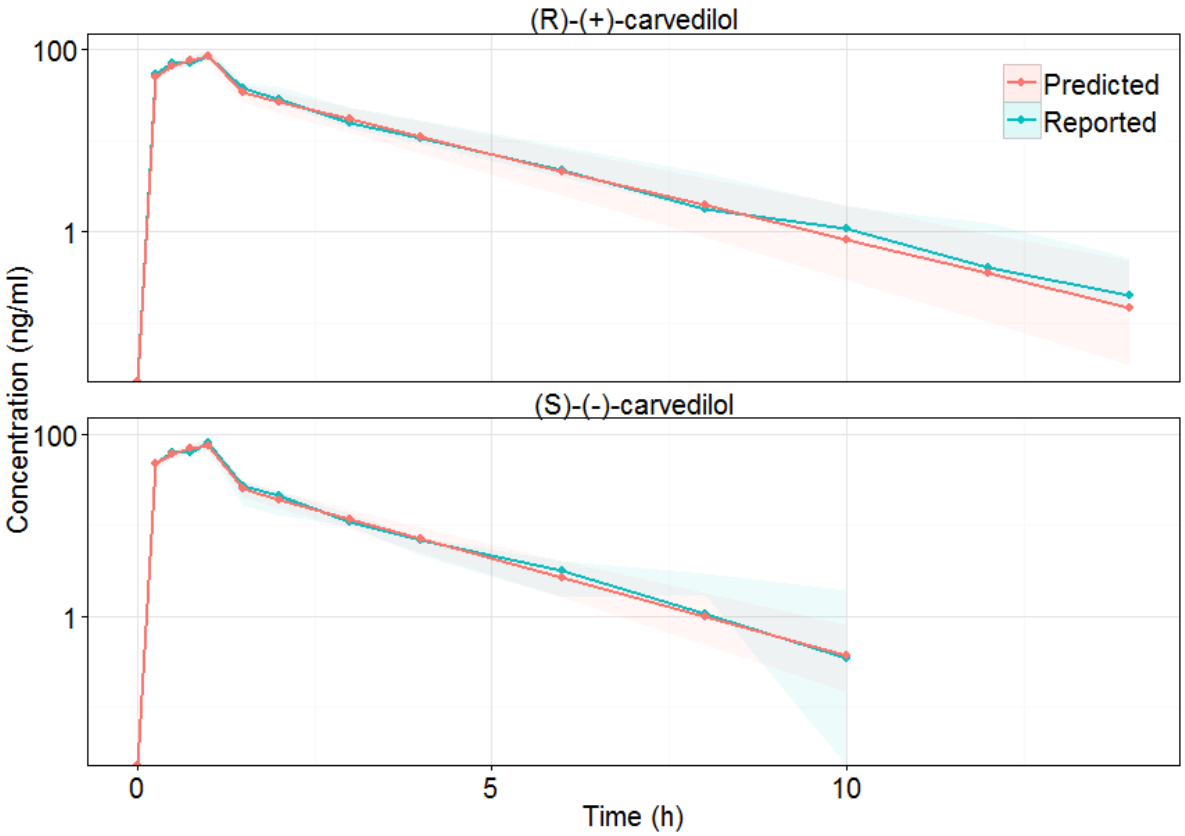


Figure S4: Visual predictive check (VPC) of carvedilol enantiomers showing the reported and predicted carvedilol concentration vs. time profiles following a 1 h infusion of 12.5 mg racemic carvedilol. **Shaded areas**: Quartile interval for observed and predicted concentrations. **Solid lines**: The population predicted concentrations or the reported concentration medians.

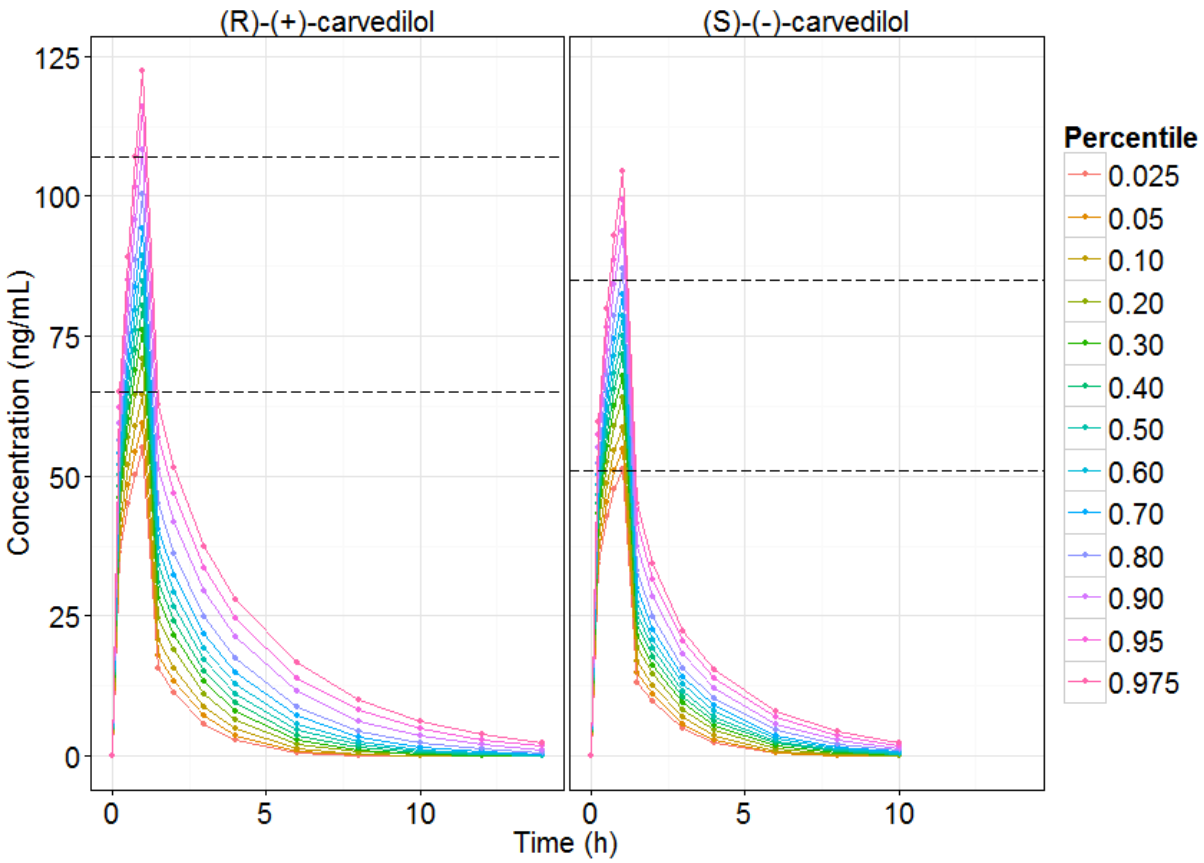


Figure S5: Simulated concentration vs. time profiles stratified by percentiles. These profiles were combined with the clinical trial data obtained after oral administration of carvedilol to healthy subjects and T2DM patients.

Table S2: Primary and secondary pharmacokinetic parameters of carvedilol as reported by Neugebauer et al. (1990), following a 1 h infusion of 12.5 mg racemic carvedilol.

Parameter	Median	Min	Max	SD	IIV
CL_R (L/h)	36.3	18.6	44.8	7.6	0.051
CL_S (L/h)	39.7	34.9	51.4	4.8	0.014
V_R	170	103	251	42.7	0.061
V_S	188	105	284	51.7	0.073
AUC_R	172	139	325	56.4	0.078
AUC_S	129	76	178	29.4	0.053

CL_S and CL_R Clearances of (S)-(-) and (R)-(+)-carvedilol. V_S and V_R: Volume of distribution of (S)-(-) and (R)-(+)-carvedilol. AUC_S and AUC_R: Area under the plasma concentration curve of (S)-(-) and (R)-(+)-carvedilol. IIV: imputed inter-individual variability.

Table S3: Pharmacokinetic model parameter estimates for carvedilol enantiomers following a 1 h infusion of 12.5 mg racemic carvedilol. IIV was imputed from the standard deviations reported in the original publication.

	Parameter	estimates	IIV	Residual Variability
(S)-(-)-carvedilol	CL (L/h)	49.8	0.053	0.0147
	V1 (L)	16.1		
	Q (L/h)	67.7		
	V2 (L)	51.7	0.073	
(R)-(+)-carvedilol	CL (L/h)	38.3	0.078	
	V1 (L)	14.9		
	Q (L/h)	72.7		
	V2 (L)	50.1	0.061	

CL: Clearances. V2: peripheral volume of distribution, V1: Central volume of distribution, Q: inter-compartmental clearance.