

Table 1: Parameter estimates and bootstrap of fixed and random effects from the final (S)-(-)-carvedilol and its metabolites pharmacokinetic model

Parameter		Population estimates				Bootstrap			
		PK parameters Typical value 95% CI	RSE (%)	IIV	RSE (%)	PK parameters Median 95% CI	CV (%)	IIV Median 95% CI	CV (%)
Ka (h ⁻¹)		0.98 (0.46-2.21)	9.44	0.25	15.26	0.94 (0.78-1.18)	10.81	0.24 (0.17-0.34)	16.19
Residual CI (L/h)		28.15 (20.11-41.73)	23.21	0.15	17.57	28.16 (23.45-33.81)	14.25	0.16 (0.11-0.22)	16.78
F (%)		16.43 (7.03-29.58)	16.74	0.234	17.68	14.14 (11.02-17.30)	19.25	0.22 (0.16-0.32)	16.47
Vc (L)		35.93 (19.59-84.14)	12.71	0.29	16.24	35.92 (27.38-47.10)	14.61	0.29 (0.15-0.41)	17.01
Q (L/h)		46.88 (28.08-66.81)	14.46	0.11	15.12	45.16 (35.32-57.28)	13.35	0.10 (0.07-0.14)	16.84
Vp (L)		105.16 (62.12-167.73)	14.51	0.55	16.24	132.66 (108.82-171.77)	12.61	0.55 (0.37-0.82)	16.54
	Healthy CYP2D6 EM	1.65 (0.97-2.84)	19.46			1.46 (1.17-2.04)	22.25		
CYP2D6 CI (L/h)	T2DM CYP2D6 EM	7.28 (1.35-20.97)	21.73	0.52	17.31	5.91 (4.64-7.33)	19.24	0.49 (0.33-0.73)	16.47
	T2DM CYP2D6 PM	0.49 --	18.37			0.41 (0.2-1.02)	20.25		
	Healthy CYP2D6 EM	16.17 (8.21-31.35)	18.64			16.17 (13.02-20.08)	20.25		
CYP2C9 CI (L/h)	T2DM CYP2D6 EM	7.71 (3.02-15.29)	17.34	0.27	18.74	6.73 (4.91-8.95)	19.27	0.27 (0.19- 0.39)	17.44
	T2DM CYP2D6 PM	13.88 --	17.70			13.74 (11.09-17.05)	21.15		
	Healthy CYP2D6 EM	45.97 (36.60-62.94)				45.98 (37.18-58.94)	10.99		
Total CI (L/h)	T2DM CYP2D6 EM	43.14 (30.03-64.07)	--	--	--	43.14 (29.62 -61.07)	22.73	--	--
	T2DM CYP2D6 PM	42.52 --				42.08 (32.94 -55.19)	13.71		
OHC CI (L/h)		40.28 --	14.02	--	--	33.85 (26.08-42.89)	15.39	--	--
OHC Vc (L)		7.15 --	17.36	--	--	6.03 (4.89 -7.53)	16.50	--	--
DMC CI (L/h)		138.67 --	17.24	--	--	138.67 (97.80-196.63)	18.42	--	--
DMC Vc (L)		27.89 --	16.24	--	--	27.84 (22.01-35.23)	17.46	--	--
σ ² proportional		0.13 --	6.17	--	--	0.13 (0.11-0.14)	6.82	--	--

RSE: relative standard error, IIV: interindividual variability; CI: confidence interval; CV: coeficiente of variation; OHC: hydroxyphenylcarvedilol; DMC: O-desmethylcarvedilol; EM: CYP2D6 extensive metaboliser; PM: CYP2D6 poor metaboliser; Ka: absorption rate constant; CI: clearance; F: bioavailability; Vc: central volume of distribution; Q: inter-compartment clearance; Vp: peripheral volume of distribution