

Table 2: Parameter estimates and bootstrap of fixed and random effects from the final (R)-(+)-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)		0.86 (0.54-1.46)	10.63	0.12	10.25	0.85 (0.75-1.02)	9.31	0.12 (0.08-0.16)	17.41
Residual CI (L/h)		4.81 (3.47-7.19)	13.86	0.11	13.57	4.19 (3.87-5.20)	15.24	0.110 (0.08-0.16)	17.54
F (%)		25.40 (16.89-51.54)	19.54	0.18	17.67	23.13 (18.49-30.20)	20.13	0.16 (0.11-0.25)	18.25
Vc (L)		21.42 (7.84-68.06)	16.88	0.67	15.41	19.63 (16.30-26.02)	16.60	0.66 (0.42-1.1)	17.91
Q (L/h)		28.52 (7.52-34.13)	12.67	0.71	18.45	28.49 (21.83-35.84)	13.99	0.18 (0.13-0.26)	17.85
Vp (L)		97.5 (64.44-151.13)	17.27	0.18	16.62	71.19 (60.33-110.12)	16.31	0.79 (0.49-1.25)	18.17
CYP2D6 CI (L/h)	Healthy CYP2D6 EM	2.69 (1.77-3.91)	18.25			3.40 (2.67-4.15)	16.25		
	T2DM CYP2D6 EM	13.70 (7.45-27.56)	15.42	0.13	18.26	6.07 (5.42-8.04)	16.41	0.11 (0.08-0.15)	16.50
	T2DM CYP2D6 PM	0.46 --	17.07			0.53 (0.30-1.05)	16.98		
CYP2C9 CI (L/h)	Healthy CYP2D6 EM	25.60 (13.95-38.00)	15.64			26.24 (19.34-33.69)	16.38		
	T2DM CYP2D6 EM	10.50 (4.85-22.41)	18.11	0.26	17.29	11.31 (9.07-14.29)	17.55	0.25 (0.16-0.35)	16.32
	T2DM CYP2D6 PM	24.35 --	17.19			28.81 (23.20-36.04)	16.00		
Total CI (L/h)	Healthy CYP2D6 EM	33.10 (20.93-44.71)				34.50 (27.26-50.11)	16.01		
	T2DM CYP2D6 EM	29.01 (19.34-44.04)	--	--	--	21.69 (17.74-26.34)	16.25	--	--
	T2DM CYP2D6 PM	29.62 --				33.88 (27.52-42.35)	16.84		
OHC CI (L/h)		31.10 --	14.08	--	--	42.87 (34.39-53.43)	15.66	--	--
OHC Vc (L)		10.05 --	16.14	--	--	9.98 (8.72-11.42)	15.45	--	--
DMC CI (L/h)		131.54 --	16.24	--	--	142.44 (102.62-197.11)	17.25	--	--
DMC Vc (L)		18.73 --	17.47	--	--	21.11 (17.24-30.84)	17.25	--	--
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