

Online Supporting Information

**Population pharmacokinetics of ramipril in patients with chronic heart failure: a real-world
longitudinal study**

Katja Čvan Trobec¹, Iztok Grabnar¹, Jurij Trontelj¹, Mitja Lainščak^{2,3}, Mojca Kerec Kos^{1*}

¹ University of Ljubljana, Faculty of Pharmacy, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia

² Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

³ Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia

*Corresponding author:

Mojca Kerec Kos

University of Ljubljana, Faculty of Pharmacy, Askerceva cesta 7, 1000 Ljubljana, Slovenia

e-mail: kerecm@ffa.uni-lj.si;

tel: +386-1-476-9669

Table S1. Parameters of the base pharmacokinetic model of ramipril.

	Estimate	RSE
Ka (h ⁻¹)	1.72	8%
CL (L/h)	176	10%
V ₁ (L)	38.6	20%
V ₂ (L)	426	18%
Q (L/h)	68.8	12%
CL _m (L/h)	10.1	8%
V _m (L)	86.3	14%
Between subject variability (BSV)		
BSV _{CL} (CV% [shrinkage])	26.3% [27%]	54%
BSV _{V1} (CV% [shrinkage])	137% [27%]	40%
BSV _{CLm} (CV% [shrinkage])	39.6 [3%]	35%
BSV _{Vm} (CV% [shrinkage])	64.9% [15%]	54%
Within subject variability (WSV)		
WSV _{CL} (CV% [shrinkage])	31.2% [25%]	22%
WSV _{CLm} (CV% [shrinkage])	13.1% [42%]	38%
WSV _{Vm} (CV% [shrinkage])	41.8% [42%]	126%
Residual variability [shrinkage]		
	[15%]	
Proportional (%)	38.6	12%
Proportional _m (%)	15.1	16%

Ka - absorption rate constant of ramipril, CL - clearance of ramipril, V₁ - volume of central compartment for ramipril, V₂ - volume of peripheral compartment for ramipril, Q - distribution clearance of ramipril, V_m - volume of distribution of ramiprilat, CL_m - clearance of ramiprilat, CV - coefficient of variation, RSE - relative standard error

Table S2. Influence of covariates associated with body size on pharmacokinetics of ramipril and ramiprilat.

Model	CL (ΔOFV)	CL_m (ΔOFV)	V₁ (ΔOFV)	V_m (ΔOFV)
WT ¹	-0.723	6.257	2.126	-0.362
WT ^{0.75}	-3.064	2.825		
FFM ¹	-3.872	1.139	0.821	-1.896
FFM ^{0.75}	-4.396	-0.680		
NFM ¹	-4.184	1.145	0.825	-1.893
NFM ^{0.75}	-4.812	-0.675		

Δ OFV – difference of objective function value; WT – body weight, FFM - fat-free mass, NFM - normal fat mass

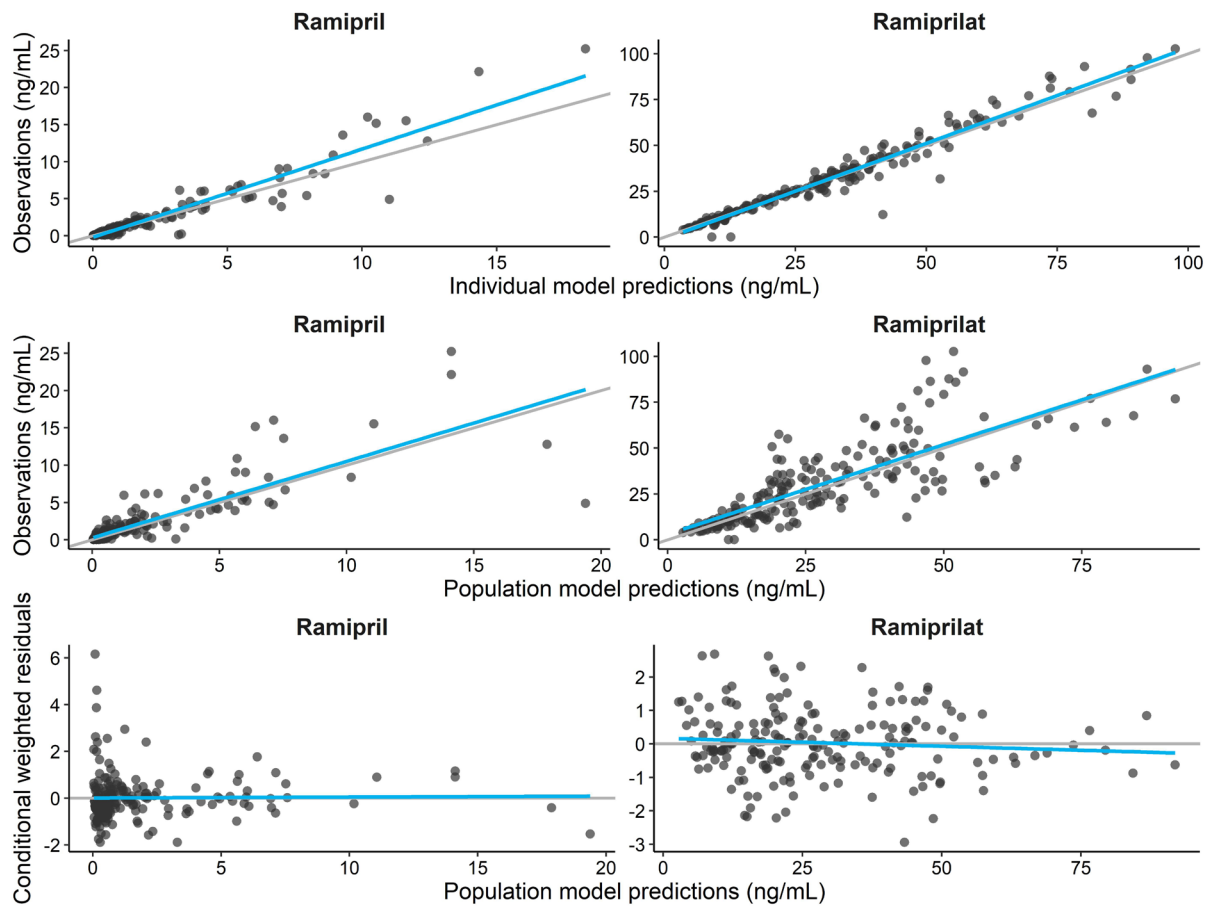


Figure S1: Standard diagnostic plots of the final population pharmacokinetic model of ramipril.

Table S3: Ramipril pharmacokinetics at the initial and follow-up study visit (N=19).

	Initial visit	Follow-up visit	Wilcoxon signed-rank test
	Median (range)	Median (range)	P-value
CL (L/h)	182.1 (79.8-322.8)	199.2 (86.0-456.7)	0.126
V ₁ (L)	40.1 (13.4-304.7)	44.6 (14.2-304.7)	0.084
V ₂ (L)	441.4 (288.7-601.1)	459.2 (290.7-599.2)	0.036
Q (L/h)	72.9 (53.0-91.9)	75.1 (53.3-91.7)	0.036
CL _m (L/h)	10.1 (5.3-24.2)	10.0 (5.0-26.6)	0.841
V _m (L)	86.4 (29.7-704.3)	68.5 (26.0-323.6)	0.117

CL - clearance of ramipril, V₁ - volume of central compartment for ramipril, V₂ - volume of peripheral compartment for ramipril, Q - distribution clearance of ramipril, V_m - volume of distribution of ramiprilat, CL_m - clearance of ramiprilat

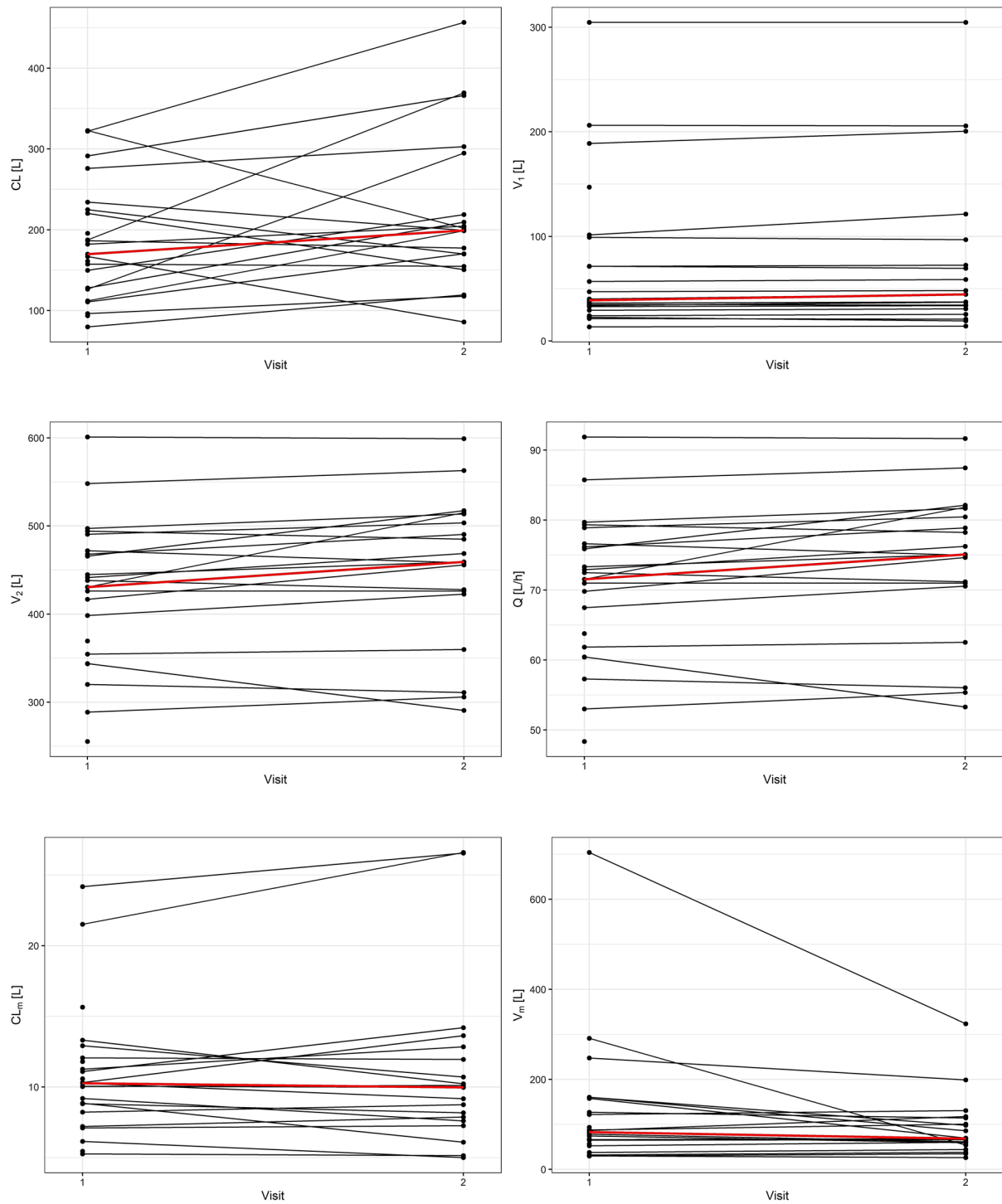


Figure S2: Changes in individual pharmacokinetic parameters (circles and black lines) of ramipril between the two study visits and median (red line).