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An Integrated PBPK-QSP Model for Statins: Implications of Transporter-Mediated Distribution

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Aims

1) Develop a PBPK-QSP model to describe statin disposition and inhibition on liver cholesterol production (Figure 1).

2) Assess the implications on PK and PD in different scenarios using the established PBPK-QSP model.

3) Investigate the factors associated with interindividual variability in statins PD using the established PBPK-QSP model.

Methods

A QSP model for the LDL lowering effect off statins was established based on a reported model on PCSK9 inhibitors [1]. Further mechanistic descriptions of statin liver cholesterol inhibition was implemented using individual LDL data from a randomized, parallel-group, open-label trial in patients (NCT00654537) [2]. Simvastatin and Pravastatin were used as investigational compounds of this exercise. The QSP model was coupled with statin PBPK model in PK-Sim/MoBi®. Population variability was included in expression of enzymes, transporters and other processes involved in statin disposition and pharmacology.

Results

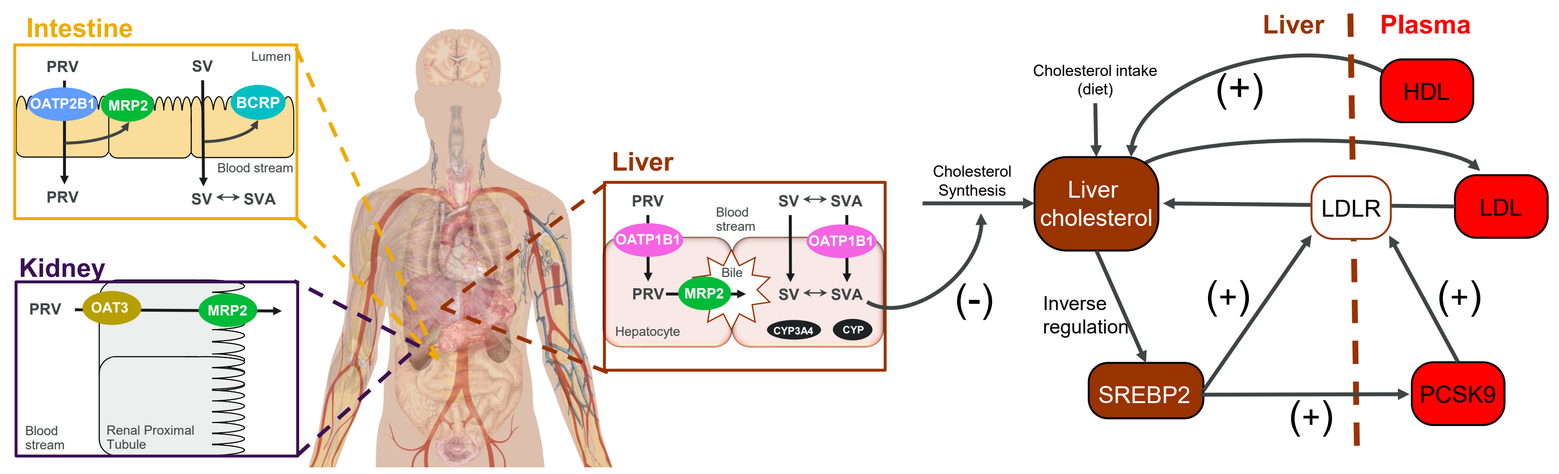
An integrated PBPK-QSP model for statins was developed in PK-Sim/MoBi that coupled the predicted unbound liver concentration to the effect of liver cholesterol inhibition. The statins PK was validated for dose range 10-80 mg (Figure 2). The QSP model, informed via 2753 measurements of circulating LDL concentrations in 1147 patients, successfully described the time course for the LDL lowering effects of the two statins (Figure 3). The model was externally validated against literature clinical studies (Figure 4). The established PBPK-QSP model was applied to predict the statin LDL lowering effect in different DDI and DGI scenarios (Figure 5) and the interindividual variability (Figure 6).

Table 1. Population estimated parameters

Parameter	SVA Estimate (95% CI)	PRV Estimate (95% CI)
I_{max}	1 (fixed)	1 (fixed)
IC_{50} (μM)	0.0012 (7E-4-1.7E-3)	0.004 (3.8E-3-4.3E-3)
gamma	0.670 (0.593-0.748)	-
IC_{50} ETA (shrinkage)	1.22 (0.057)	1.48 (0.11)
Standard deviation	0.073 (0.066-0.080)[a]	5.0 (4.6-5.5)[b]

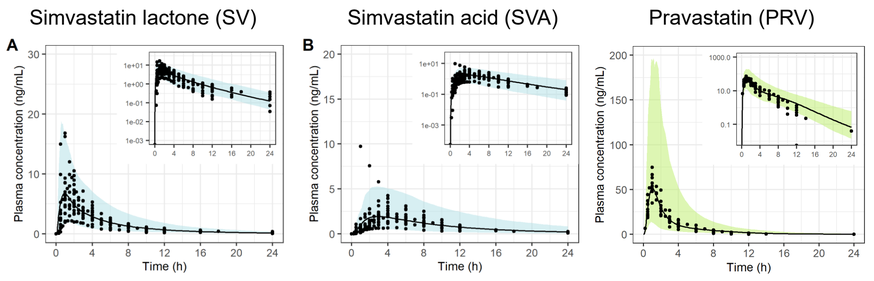
[a]multiplicative [b]additive (FOCE-ELS population); SVA: Simvastatin acid; PRV: Pravastatin

Figure 1. PBPK-QSP schematic representation for simvastatin and pravastatin



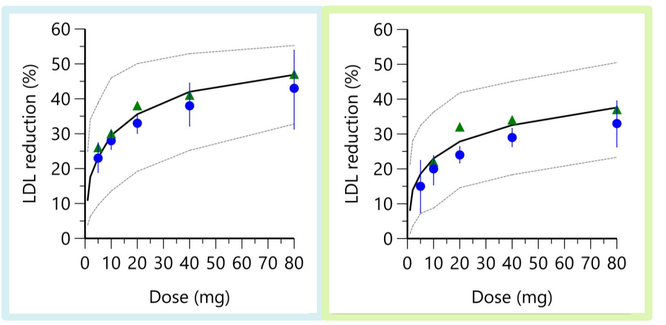
SV: Simvastatin lactone; SVA: Simvastatin acid; PRV: Pravastatin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LDLR: LDL receptor; SREBP2: Sterol Regulatory Element Binding Transcription Factor 2: PCSK9: Proprotein convertase subtilisin/kexin type 9. Inverse regulation: the lower the liver cholesterol levels the higher the SREBP2 levels (-): Inhibition; (+): Positive regulation (inhibit clearance or stimulate synthesis)

Figure 2. PBPK model validation: predicted human plasma exposure vs. observed (40mg)



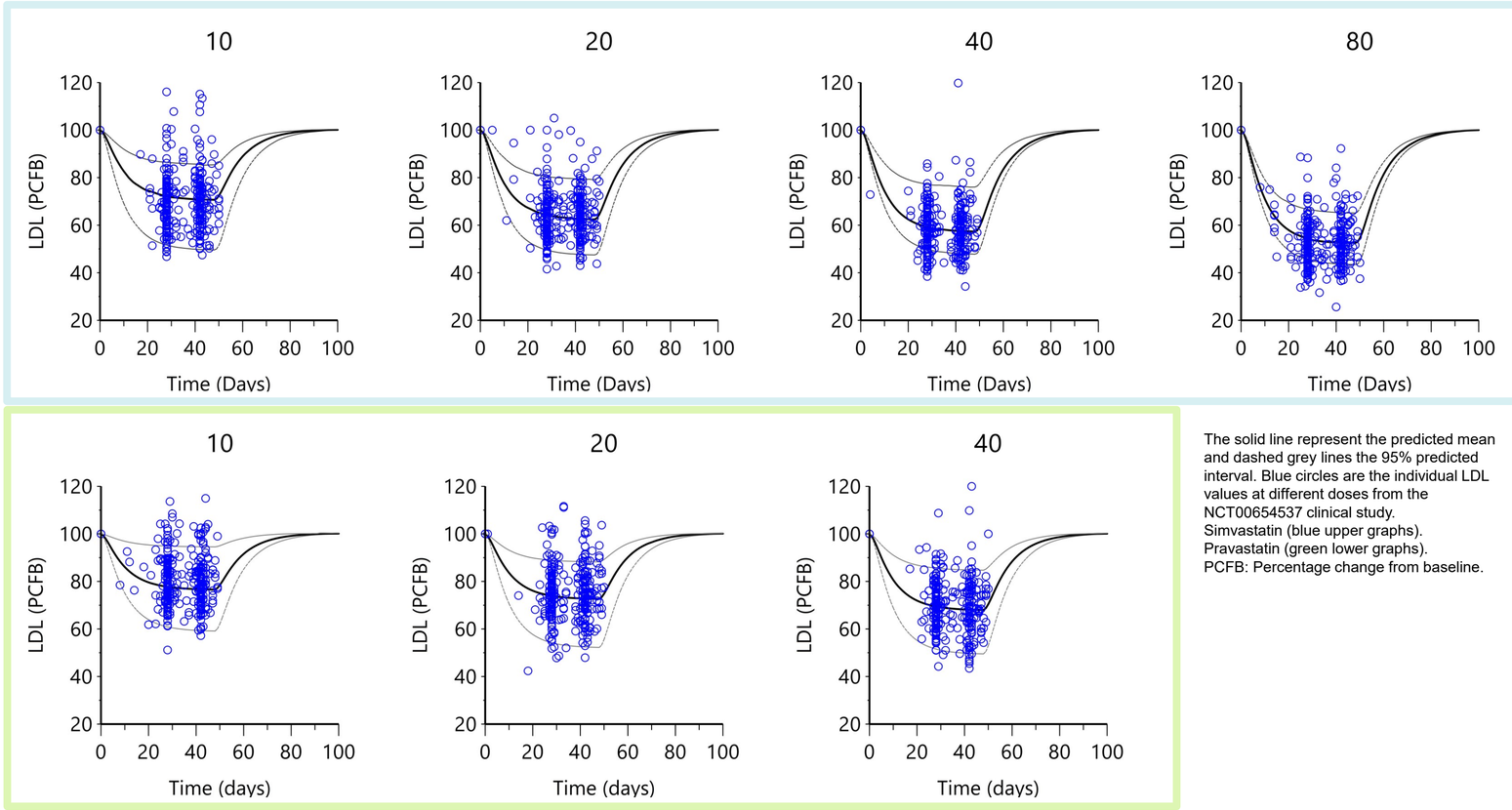
Predicted PK profiles (lines) vs. clinical observations reported as study mean (circles) for simvastatin lactone (A), simvastatin acid (B) and pravastatin (C). The solid lines represent the predicted mean and the shaded area the 90% predicted interval for virtual populations.

Figure 4. PBPK-QSP model validation: predicted LDL reduction vs. observed



The solid line represent the predicted mean and dashed grey lines the 95% predicted interval for virtual populations. Blue circles is the meta-analysis reported mean and 95% CI [3] and the green triangles the reported mean in the respective FDA label.

Figure 3. PBPK-QSP simulated vs. individual observed statin LDL-lowering effects



The solid line represent the predicted mean and dashed grey lines the 95% predicted interval. Blue circles are the individual LDL values at different doses from the NCT00654537 clinical study.
Simvastatin (blue upper graphs).
Pravastatin (green lower graphs).
PCFB: Percentage change from baseline.

Figure 5. PBPK-QSP: PK-PD Application

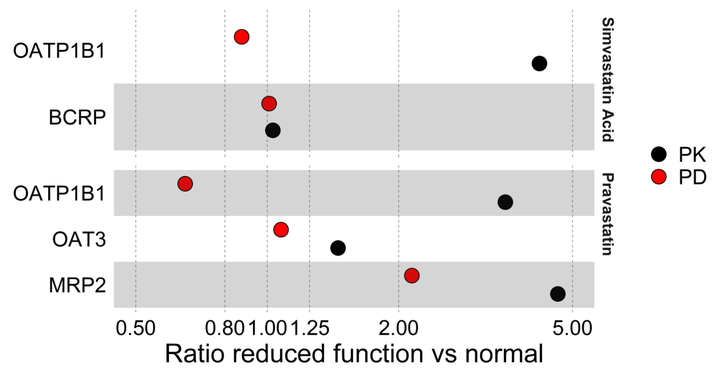
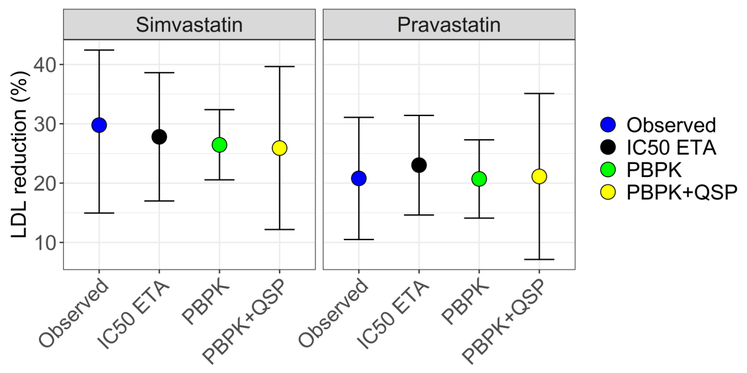


Figure 6. PBPK-QSP: Population variability



Circles represent mean and error bars the standard deviation for LDL reduction at 10 mg dose.
IC50 ETA: model with variability only in IC50 parameter (fitted value)
PBPK: model with variability only in physiological parameters
PBPK+QSP: model with variability in physiological and pharmacological parameters (except statin inhibition)

References

[1] Gadkar K et. al. CPT Pharmacometrics Syst Pharmacol. 2014 Nov 26;3(11):e149.
[2] Jones PH et. al. Am J Cardiol. 2003 Jul 15;92(2):152-60.
[3] Law 2014Law MR et. al. BMJ. 2003 Jun 28;326(7404):1423.