

A Physiologically Based Pharmacokinetic Model for Open Acid and Lactone Forms of Atorvastatin and Its Two Metabolites

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OBJECTIVES

The aim of this work was to develop a full PBPK model for atorvastatin (ATS) and its metabolites (open acid and lactone forms) able to quantitatively assess the impact of OATP1B1 phenotypes on ATS C_{max} and AUC.

METHODS

The model has been developed in the PBPK platform Simcyp® Simulator V19 following a “bottom-up” approach. The workflow followed to develop and validate the model as well as the model structure are illustrated in **Figures 1** and **2**, respectively.

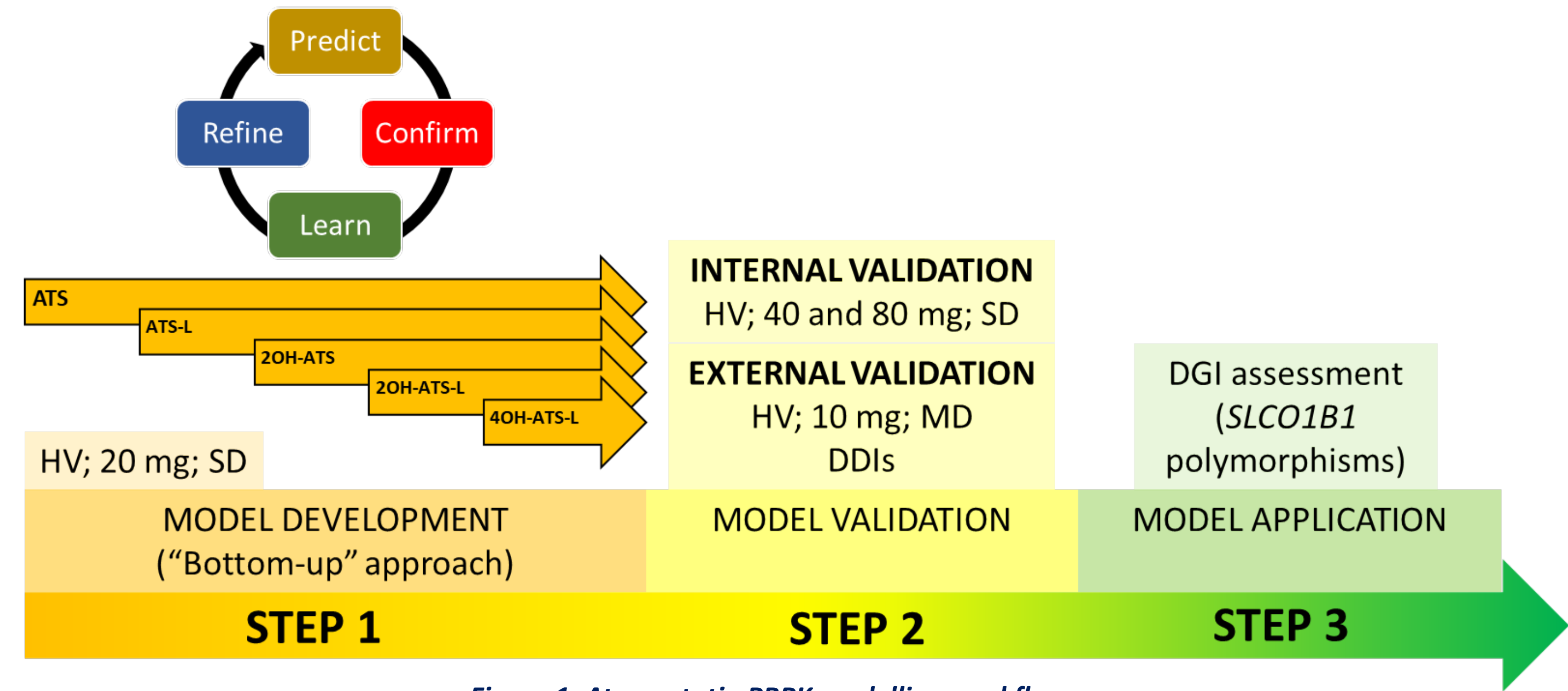


Figure 1. Atorvastatin PBPK modelling workflow.

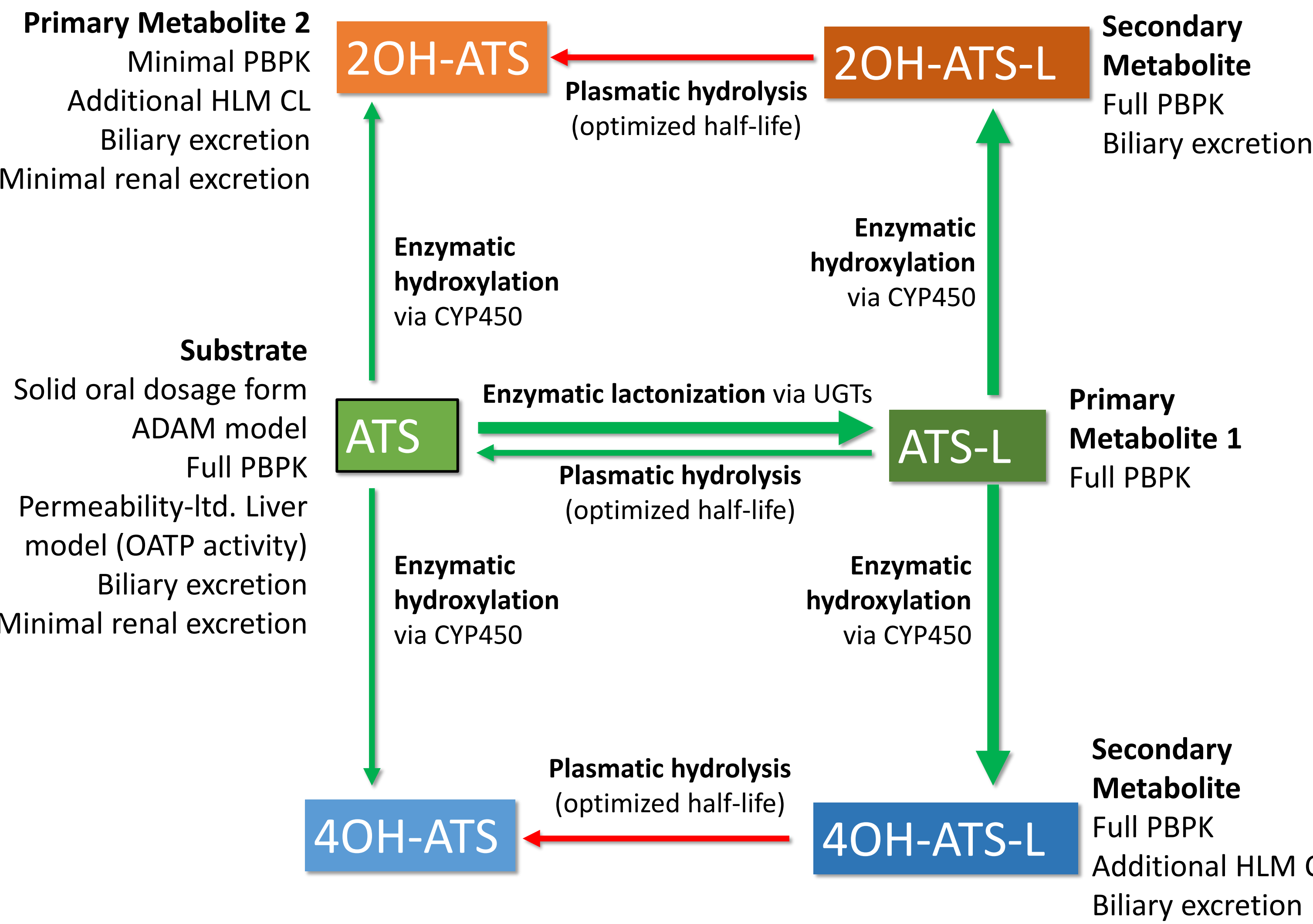


Figure 2. Atorvastatin PBPK model structure.

RESULTS

Table 1 shows the exposure PK parameters for all the metabolites in both PBPK model development (20 mg dose level) and validation (10, 40 and 80 mg dose levels) steps. The ATS-Ca PBPK model developed was able to properly describe clinically relevant DDIs with both CYP3A4 and OATPs inhibitors. **Table 2** summarizes the predicted exposure (AUC and C_{max}) changes in ATS and ATS-L as well as the predicted/observed ratio.

Table 1. Prediction errors in AUC and C_{max} for ATS, ATS-L, 2OH-ATS, 2OH-ATS-L and 4OH-ATS-L in each model development step.

	Analyte	Dose (mg)	Regimen	AUC Prediction Error	C_{max} Prediction Error
Step 1	ATS	20	SD	1.33 ✓	0.87 ✓
	ATS-L	20	SD	0.89 ✓	1.67 ✓
	2OH-ATS	20	SD	0.57 ✓	0.33 ✗
	2OH-ATS-L	20	SD	1.01 ✓	0.79 ✓
	4OH-ATS-L	20	SD	1.44 ✓	1.05 ✓
Step 2a	ATS	40	SD	1.58 ✓	1.07 ✓
	2OH-ATS	40	SD	0.56 ✓	0.30 ✗
	ATS	80	SD	1.21 ✓	0.85 ✓
	2OH-ATS	80	SD	0.52 ✓	0.26 ✗
Step 2b	ATS	10	MD	0.86 ✓	1.17 ✓
	2OH-ATS	10	MD	0.64 ✓	0.73 ✓

Table 2. Predicted and observed changes in AUC and C_{max} of ATS and ATS-L after concomitant administration of different perpetrators of DDIs.

Perpetrator/ Victim	AUC ratio			C_{max} ratio		
	Observed	Predicted	Ratio P/O	Observed	Predicted	Ratio P/O
Itraconazole						
ATS	3.31 ^a	2.20 ^a	0.66	1.2 ^c	1.19 ^c	0.99
	3.11 ^b	2.08 ^b	0.67			
ATS-L	3.98 ^a	3.84 ^a	0.96	2.26 ^c	2.72 ^c	1.20
	4.11 ^b	3.85 ^b	0.94			
Rifampin						
ATS	7.25 ^a	5.74 ^a	0.79	10.46 ^c	6.35 ^c	0.61
Clarithromycin						
ATS	3.08 ^d	2.90 ^d	0.94	2.16 ^e	1.89 ^e	0.88
ATS-L	2.67 ^d	3.86 ^d	1.45	1.5 ^e	2.04 ^e	1.36

^a: for AUC_{0-inf} mean values; ^b: for AUC₀₋₇₂ mean values; ^c: for C_{max} mean values; ^d: for AUC₀₋₄₈ geometric mean values; ^e: for C_{max} geometric mean values

Results of the evaluation of the impact of OATP1B1 activity in ATS CL, AUC and C_{max} are shown in **Table 3** and **Figure 3**. The analysis revealed a statistically significant difference in ATS CL ($p < 0.01$), as poor transporters (PT) have a 30% lower clearance than extensive transporters (ET) individuals. Consequently, ATS AUC and C_{max} are increased by 40 and 33% ($p < 0.05$), respectively, in individuals carrying *SLCO1B1**5 allele.

Table 3. Comparison of ATS exposure in extensive and poor transporters for OATP1B1 activity.

	ET (wild type)	PT (<i>SLCO1B1</i> *5)	Fold change	p-value
AUC ₀₋₄₈ (mg/L·h)	0.08677	0.12160	1.40	0.01836
C_{max} (mg/L)	0.01568	0.02086	1.33	0.01094
CL (DOSE/AUC)	593.47	414.36	0.70	0.008537
N (%)	304 (60.8)	16 (3.2)	-	-

ET: extensive transporter; PT: poor transporter; AUC₀₋₄₈: truncated area under the concentration time profile; C_{max} : maximum concentration; CL: clearance; N: number of individuals

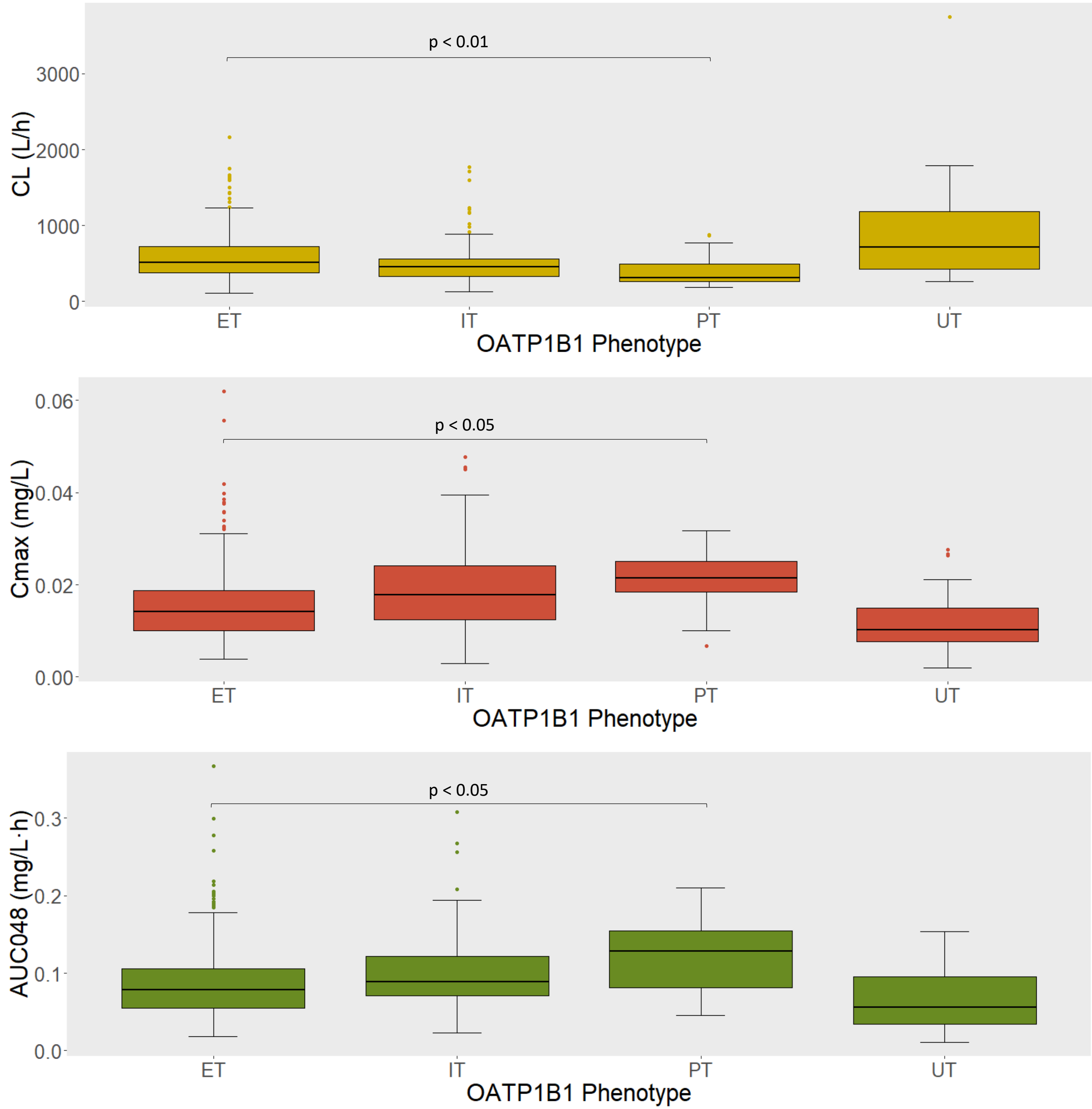


Figure 3. Impact of OATP1B1 phenotype in ATS clearance, C_{max} and AUC.

DISCUSSION AND CONCLUSION

The PBPK model here presented is able to reproduce the PK of ATS, ATS-L, 2OH-ATS-L and 4OH-ATS-L. The model has been externally validated with clinical data from DDI trials with CYP450 and OATP inhibitors. Overall, these results suggest that enzymatic lactonization plays a determinant role in ATS PK and confirms the main elimination route for this statin (lactonization, hydroxylation and hydrolysis). ATS exposure has been quantitatively assessed in different OATP1B1 phenotypes and confirmed that poor transporters (carrying *SLCO1B1**5 allele) are at higher risk of suffering statin induced myopathies (SIMs) because of a 30% lower clearance than extensive transporters. This result is consistent with the previously reported hazard ratio of 1.4 (95% CI 1.1-1.7, $p = 0.02$) for suffering SIMs [1].

References

[1] Voora, D.; Baye, J.; Mcdermaid, A.; Narayana Gowda, S.; Wilke, R.A.; Nicole Myrmoe, A.; Hajek, C.; Larson, E.A. *SLCO1B1**5 Allele is Associated with Atorvastatin Discontinuation and Adverse Muscle Symptoms in the Context of Routine Care. Clin Pharma and Therapeutics 2022.

Acknowledgements

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