

A Physiologically Based Pharmacokinetic Model of Atorvastatin and Its Metabolites Incorporating Acid–Lactone Interconversion

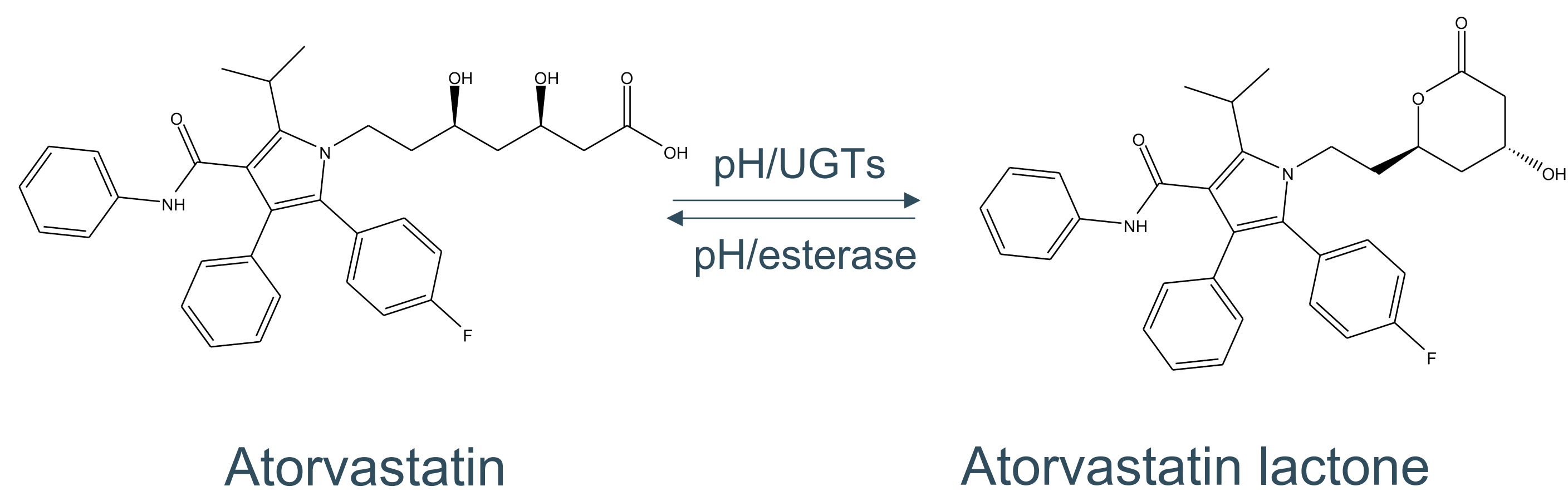
Chen Ning¹ and Pieter Annaert^{1,2}

¹Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; ²BioNotus CommV, Niel, Belgium

Introduction

- Atorvastatin is one of the most widely prescribed hydroxymethylglutaryl-CoA reductase inhibitors for managing hyperlipidemia.[1] It is administered orally in its acid form but undergoes reversible, pH-dependent lactonization under physiological conditions.[2]
- UDP-glucuronosyltransferases (UGTs)-mediated atorvastatin lactonization is a critical first step preceding extensive CYP3A4-mediated metabolism.[3]
- Elevated plasma exposure to the lactone metabolites and loss-of-function organic anion transporting polypeptide 1B1 (OATP1B1) transporter alleles have been significantly associated with an increased risk of myotoxicity.[4, 5]
- The dynamic pH-dependent and UGT-mediated conversions between these forms, together with subsequent metabolic transformations and disposition, complicate the characterization of atorvastatin's pharmacokinetic profile and the prediction of its side effects.

Figure 1. Interconversion between atorvastatin and atorvastatin lactone.



Objective

- To develop a PBPK model to predict the concentrations of atorvastatin (ATV), atorvastatin lactone (LAC), 2-hydroxy atorvastatin (2ATV) and 2-hydroxy atorvastatin lactone (2LAC), incorporating comprehensive metabolism and transport kinetics, as well as nonenzymatic interconversion.
- To evaluate the drug-drug interactions (DDIs) and drug-gene interactions (DGIs) risks associated with atorvastatin administration.

Methods

- The PBPK model was developed using PK-Sim[®] (version 12, www.open-systems-pharmacology.org)[6]. Data for the model development were sourced from literature, encompassing physicochemical properties, formulation, metabolism and transport kinetics, and plasma concentration-time profiles for atorvastatin and its metabolites.
- Clinical pharmacokinetic data from 37 clinical trials and 916 subjects from Europe, East Asia and America including C_{max} and AUC values for atorvastatin and its metabolites were compiled and divided into training (20 profiles) and verification datasets (59 profiles).
- Acid-lactone interconversion kinetics for ATV-LAC and 2ATV-2LAC were experimentally determined in biorelevant media and incorporated in the PBPK model.
- Model prediction performance was evaluated by comparing the predicted to observed time-concentration profiles, and the C_{max} and AUC values. The relative activity of OATP1B1 polymorphic forms were incorporated into the model to evaluate pharmacokinetics in different allele carriers.[7] Additionally, DDI risks were assessed for atorvastatin when co-administered with clarithromycin, gemfibrozil, and itraconazole using validated perpetrator models. [8,9]

Results

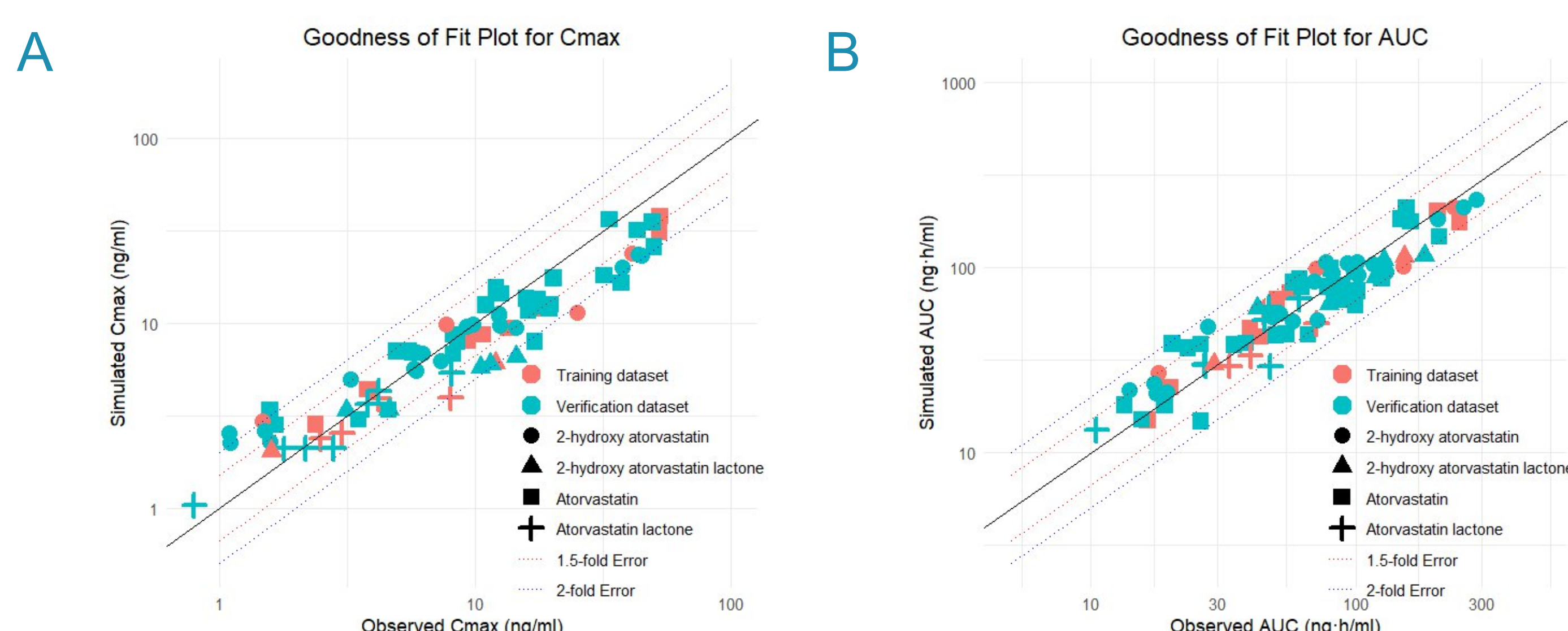


Figure 2. Predictive performance plots for C_{max} (A) and AUC (B) of atorvastatin and its metabolites in plasma. The solid black line represents the line of identity. The red and blue dotted lines indicate the 1.5-fold and 2-fold error boundaries, respectively.

Results

Table 1. Prediction errors of C_{max} and AUC of atorvastatin and its metabolites.

	C _{max}				AUC			
	ATV	LAC	2ATV	2LAC	ATV	LAC	2ATV	2LAC
Average fold error	0.88	0.89	0.96	0.67	1.01	1.00	1.05	0.86
Absolute average fold error	1.37	1.2	1.45	1.61	1.26	1.21	1.25	1.29
Prediction within 1.5-fold error	76%	75%	54%	43%	86.5%	92%	88%	86%
Prediction within 2-fold error	92%	92%	88%	86%	100%	100%	100%	100%

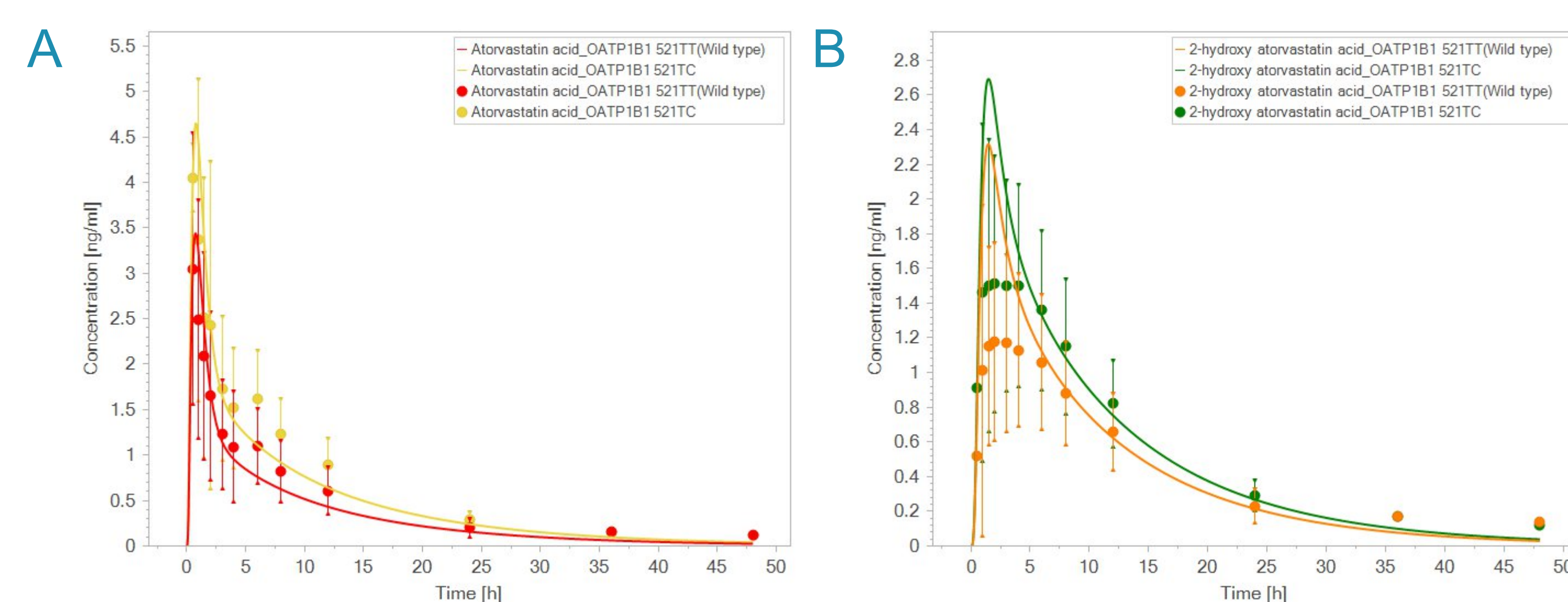


Figure 3. Predicted plasma concentration-time profiles of atorvastatin (A) and atorvastatin lactone (B) in subjects carrying the OATP1B1 c.521T>C polymorphism following a single oral dose of 10 mg. (Clinical data obtained from [7]).

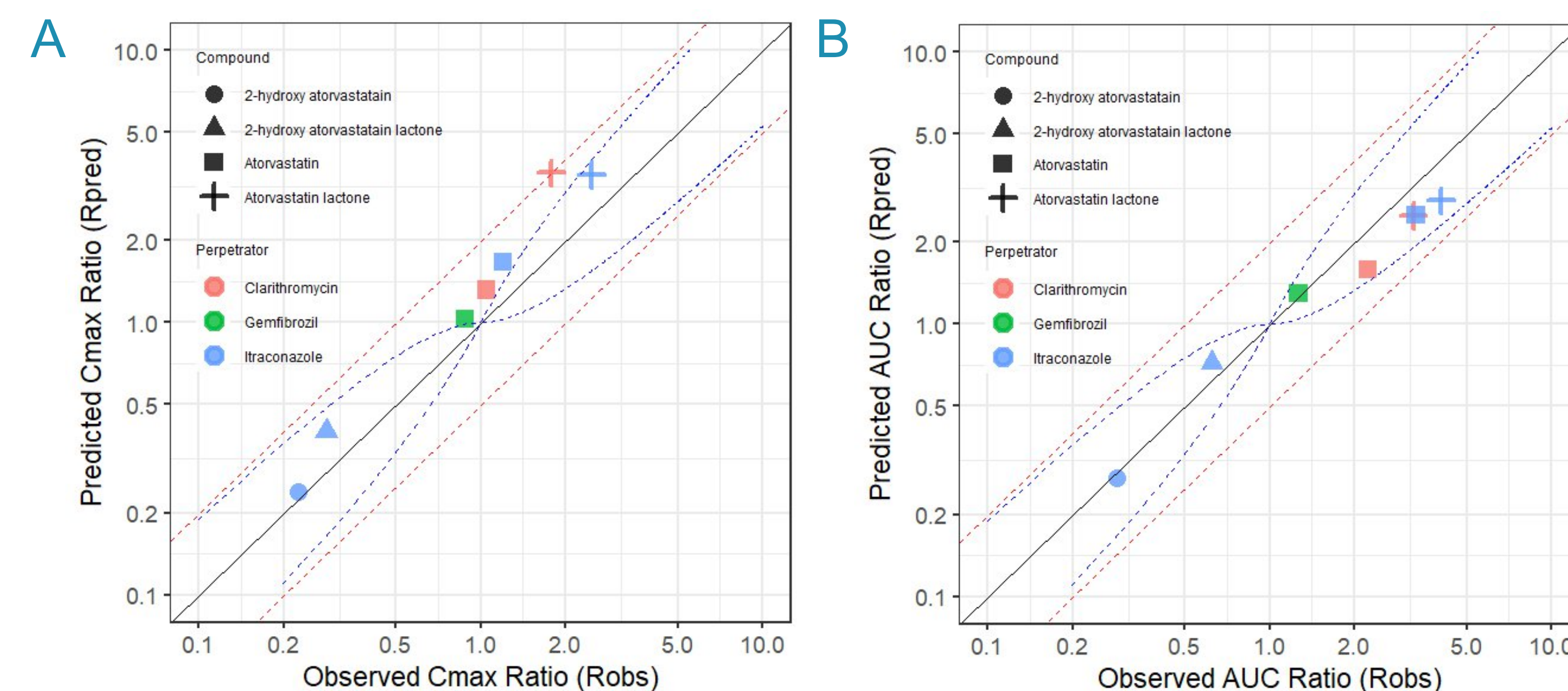


Figure 4. Predicted DDI ratios of C_{max} (A) and AUC (B) for atorvastatin and its metabolites when co-administered with clarithromycin, gemfibrozil, or itraconazole. The solid black line represents the line of identity. The dashed red and blue lines indicate the 2-fold error boundaries and the predictive limits proposed by Guest et al. [10].

Conclusion

- ✓ A physiologically based pharmacokinetic (PBPK) model was successfully developed to predict the pharmacokinetics of atorvastatin, including both the parent compound and its primary metabolites.
- ✓ The model effectively captured the impact of OATP1B1 polymorphism on systemic exposure, reinforcing the critical role of hepatic uptake transport via OATP1B1 in atorvastatin disposition and supporting the model's mechanistic credibility.
- ✓ While the model slightly underpredicted the C_{max} of 2-hydroxy atorvastatin and its lactone form, this may reflect limitations in current knowledge of their specific metabolic pathways or elimination processes, warranting further investigation.

Reference

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