Drug metabolism and Pharmacokinetics/PK Sciences

# EVALUATION OF DRUG-DRUG INTERACTION POTENTIAL BETWEEN SACUBITRIL/VALSARTAN (LCZ696) AND STATINS USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

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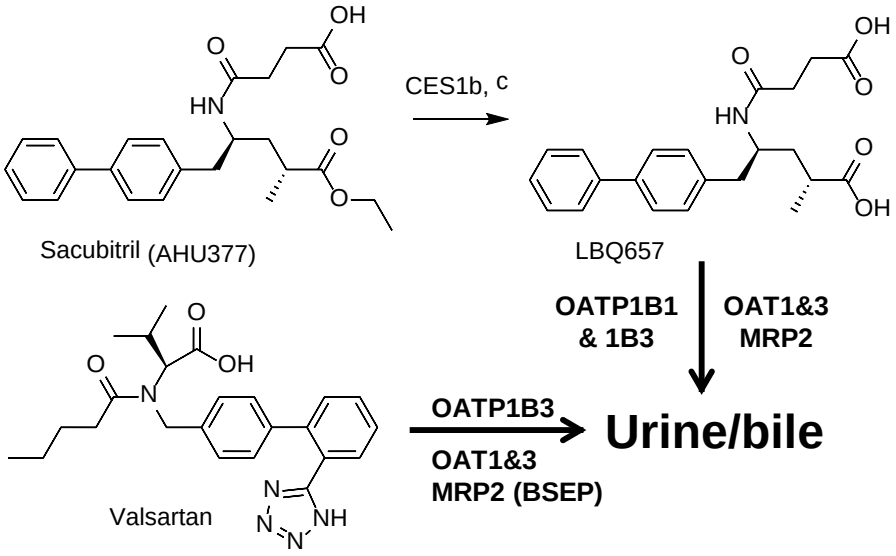
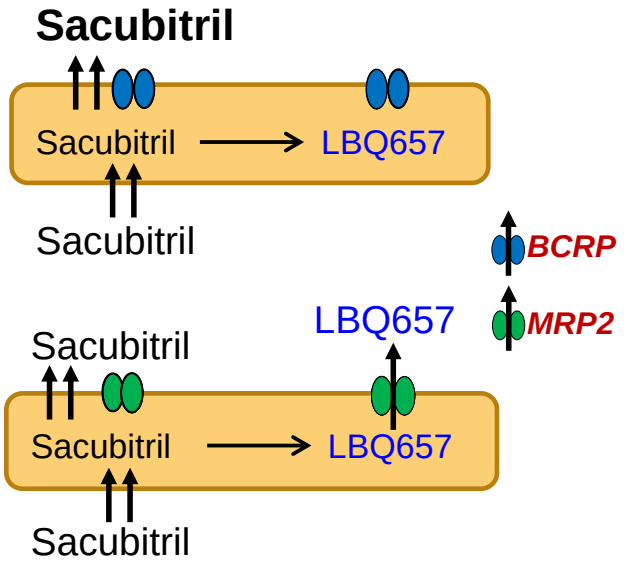
# Introduction

- LCZ696 (sacubitril/valsartan) has been shown to offer superior clinical benefits (reduced mortality & hospitalizations) to Heart Failure patients compared to the standard of care (enalapril).
- Sacubitril was shown to be an OATP1B1 and OATP1B3 inhibitor *in vitro*
  - Static predictions estimated a change in exposure in excess of 125% for sensitive OATP1B1 substrates
  - Co-administration with atorvastatin showed ~2-fold increase in atorvastatin Cmax; exposure (AUC) to atorvastatin (or its metabolites) was not significantly increased (<34%)
  - In a separate investigation, no change in simvastatin pharmacokinetics was observed when co-administered with LCZ696
- A physiological-based pharmacokinetic modeling approach was developed to explore atorvastatin and simvastatin interactions with LCZ696
- Additional modeling was done to evaluate the statin-specific DDI risk due to OATP inhibition by LCZ696

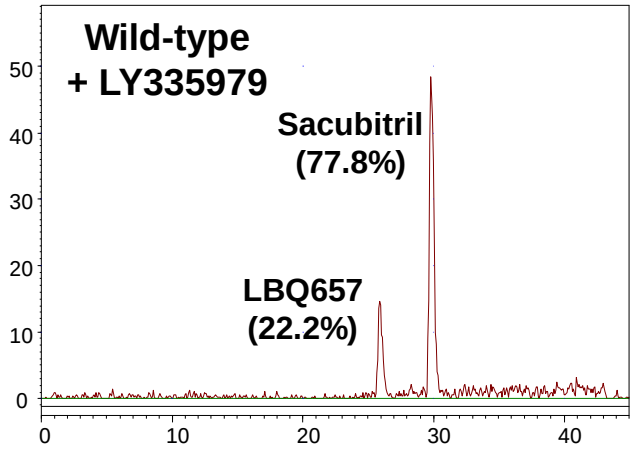
# LCZ696(sacubitril/valsartan) Disposition

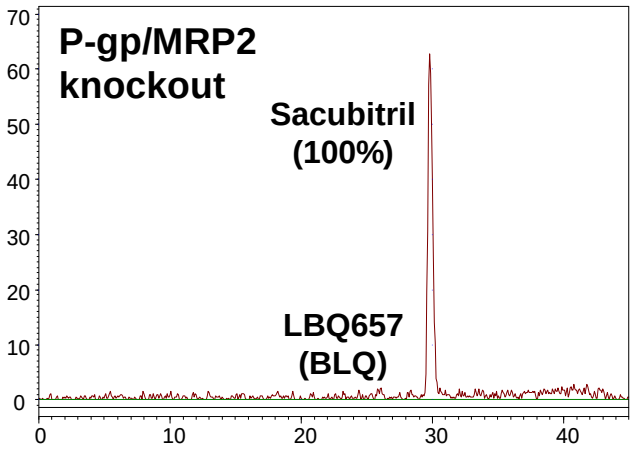
*Hydrolysis and transport across polarized cell monolayers*

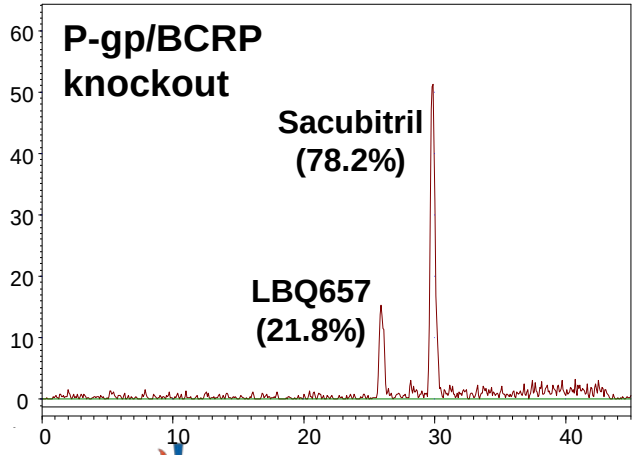



## Basolateral to Apical Transport



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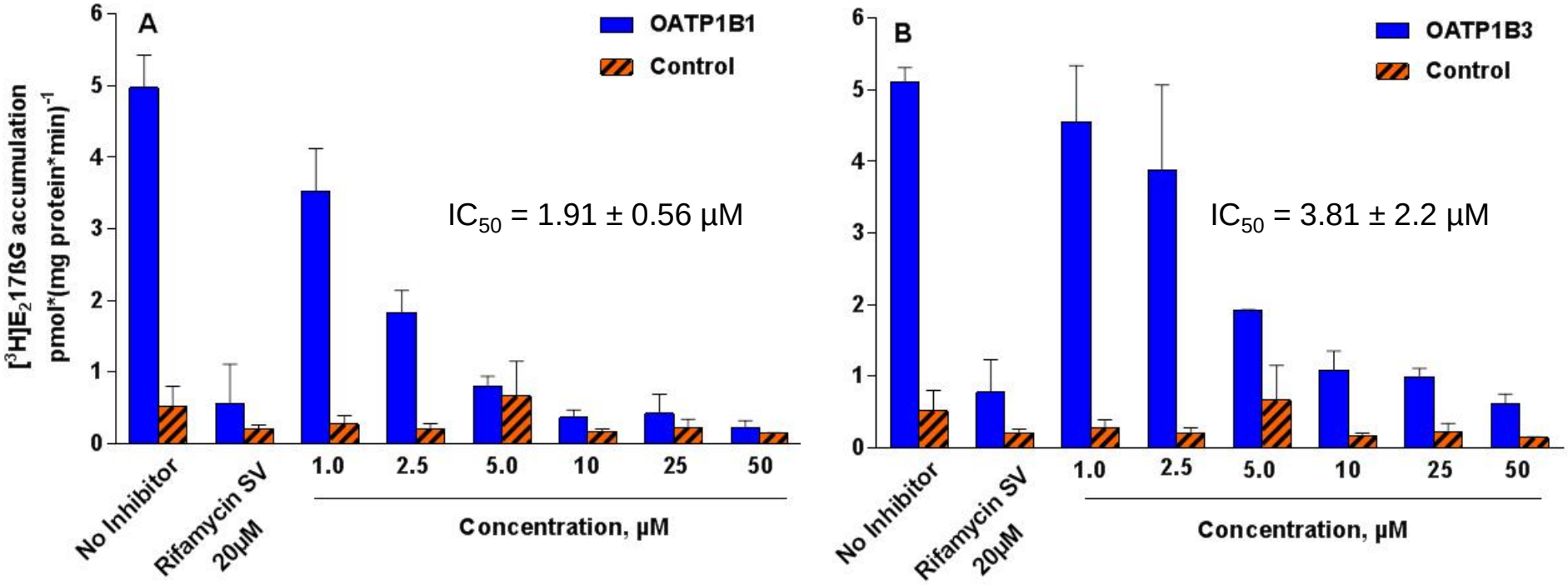
*Hanna et al., (2017) Xenobiotica, In press*

# Sacubitril OATP inhibition

*Equipotent OATP1B1/OATP1B3 inhibition*




| Dose (mg) | plasma unbound fraction | $I_{inlet,max}$ unbound, µM |
|---|---|---|
| 100 | 0.030 | 0.642 |

Static Predictions ΔAUC
OATP1B1 inhibition ~1.29
OATP1B3 inhibition ~1.15



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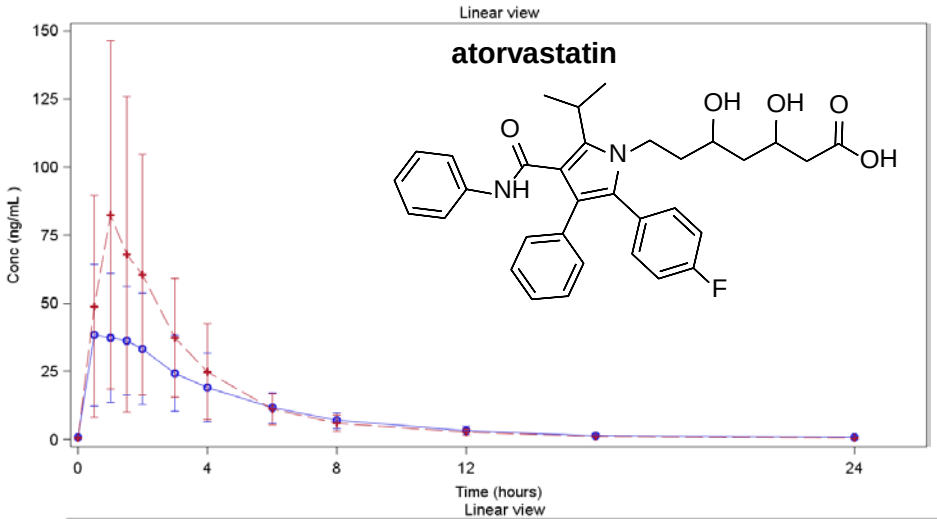
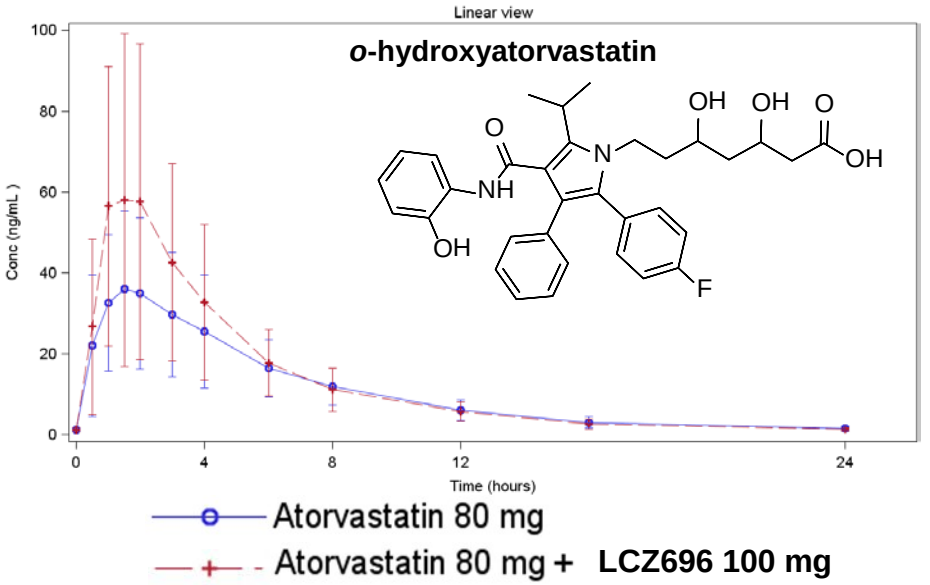
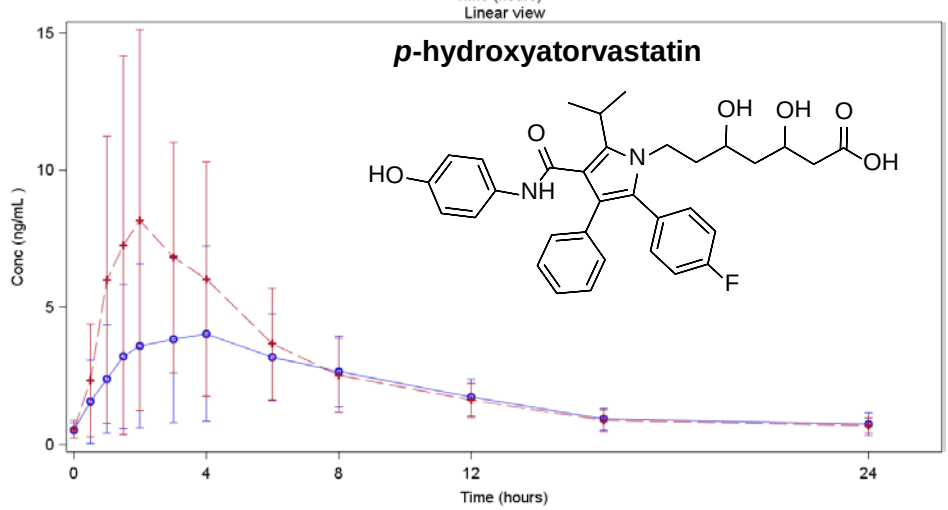
*Ayalasomayajula et al. (2016) J. Clin Pharm Ther. 41(4): 424-431*

# Effect of LCZ696 on the pharmacokinetics of atorvastatin and its metabolites




| Analyte | Geometric Mean Ratio (90% CI) | |
|---|---|---|
| | $C_{max}$ | AUC |
| Atorvastatin | **1.74** (1.49 – 2.02) | **1.34** (1.23 – 1.45) |
| *p*-hydroxy | **1.68** (1.49 – 1.91) | **1.22** (1.12 – 1.32) |
| *o*-Hydroxy | **2.08** (1.75 – 2.49) | **1.26** (1.15 – 1.39) |



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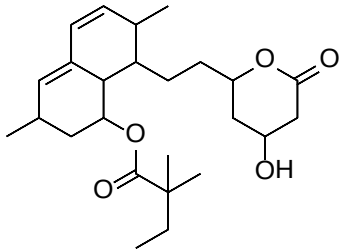
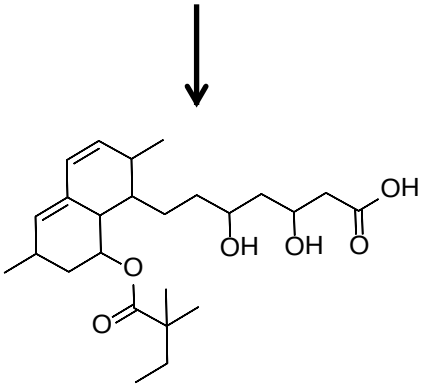
*Ayalasomayajula 2016, Eur J Drug Metab Pharmacokinet, In press*

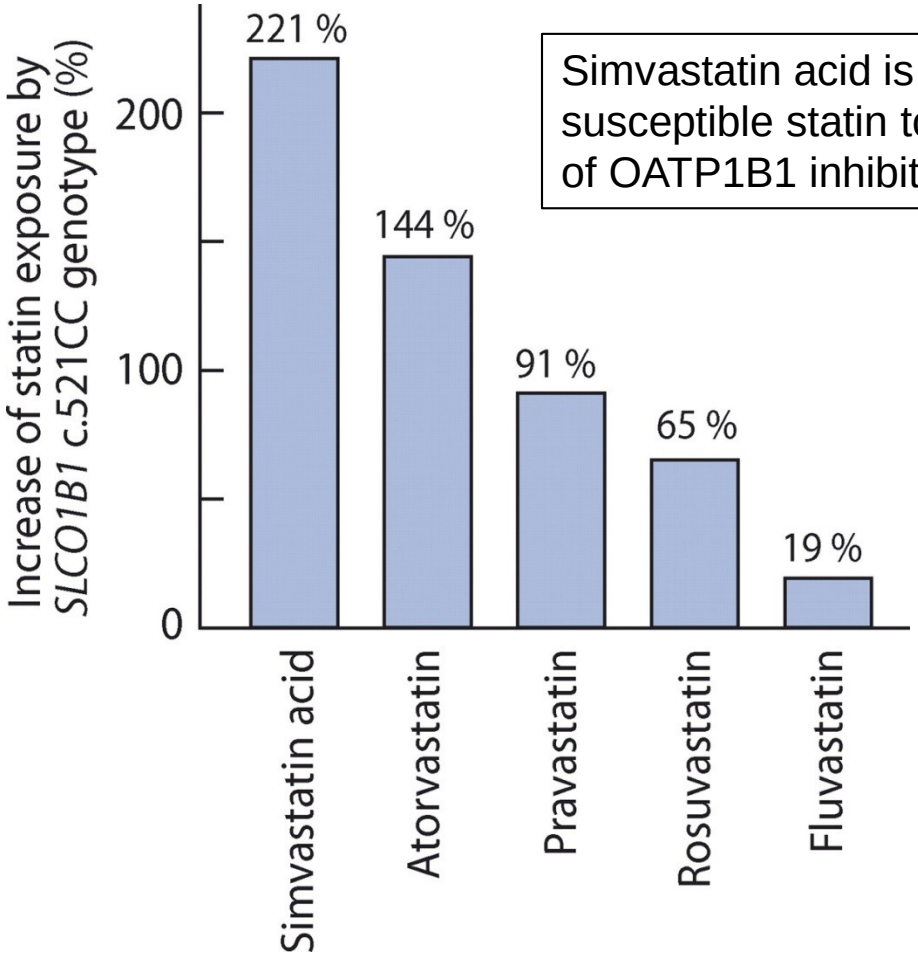
# Effect of OATP1B1 polymorphism (reduced activity) on statin exposure



Simvastatin lactone
*(inactive)*



Simvastatin acid (SVA)
*(active)*




Simvastatin acid is the most susceptible statin to DDIs as a result of OATP1B1 inhibition



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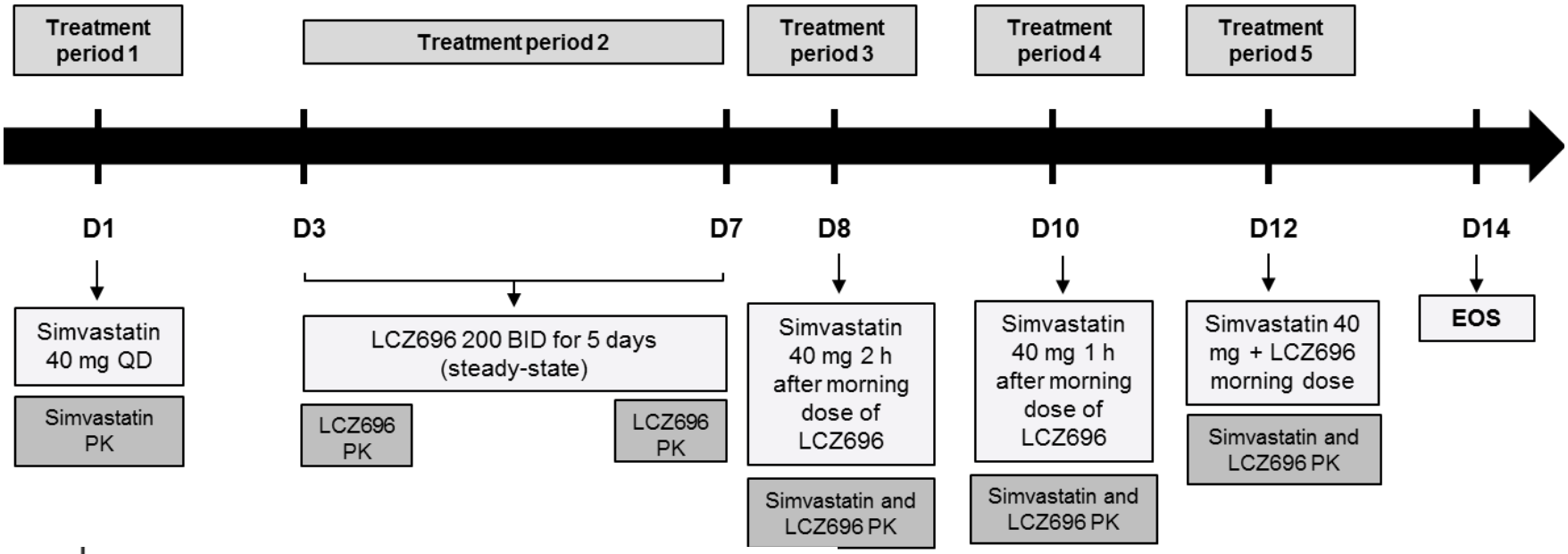
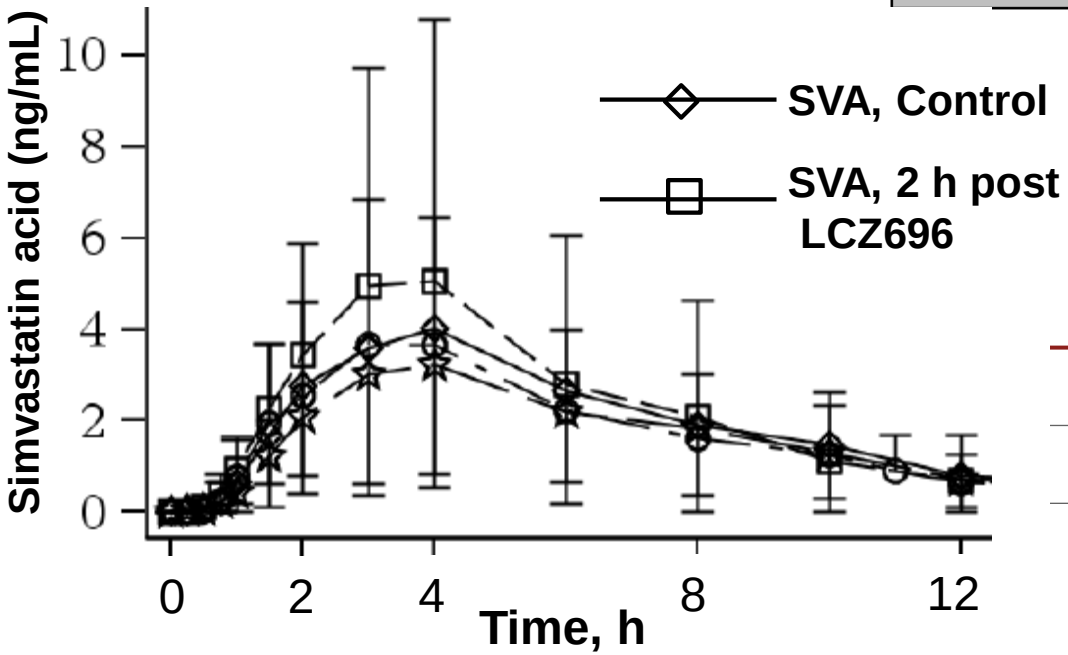
*Niemi et al 2011 Pharm rev. 63:157*

# Effect of LCZ696 on SVA Pharmacokinetics




| SVA, 2h post LCZ696 | Fold change, (90% CI) |
|---|---|
| $C_{max}$ | **1.16** (1.00-1.35) |
| $AUC_{last}$ | **1.01** (0.88-1.17) |

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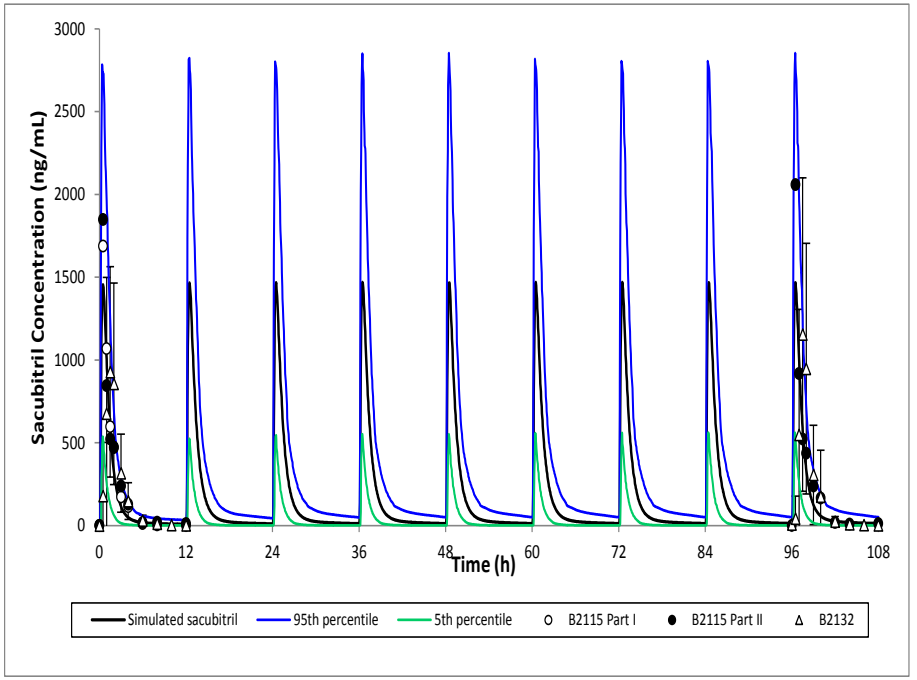
*Ayalasomayajula et al., 2016, J Clin Pharm Ther., 41, 424–431*

# Sacubitril PK prediction

*Combined bottom-up and top-down approach Simcyp (Version 15 release 1)*

| Parameter | Value | Reference |
|---|---|---|
| **Absorption (First order absorption model)** | | |
| Papp, cm/s | 3.87 × $10^{-6}$ | Caco-2 permeability |
| Tlag (h) | 0.14 | Optimized to fit clinical PK |
| ka ($h^{-1}$) | 1.3 | |
| $Q_{gut}$ (L/h) | 7.48 | Simcyp predicted |
| **Distribution (minimal PBPK)** | | |
| Vss | 0.253 | |
| **Elimination (in vivo)** | | |
| CLiv (l/h) | 27 | User defined |
| Cl renal | 0 | minimal unchanged sacubitril in urine |
| **Interaction** | | |
| OATP1B1 $IC_{50}$, | 1.91 µM | *Hanna et al, 2017* |




Healthy volunteer population (10 trials, 10 subjects per trial)
Observed data from 3 clinical trials shown as data points



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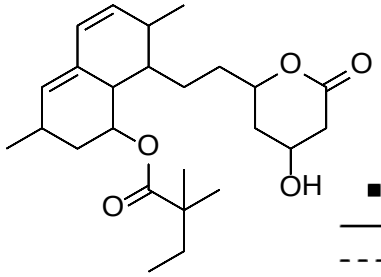
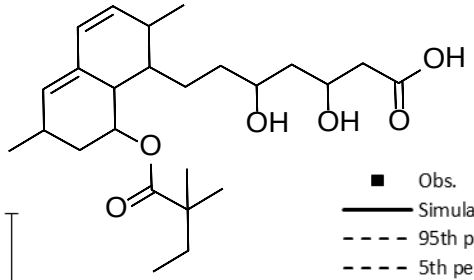
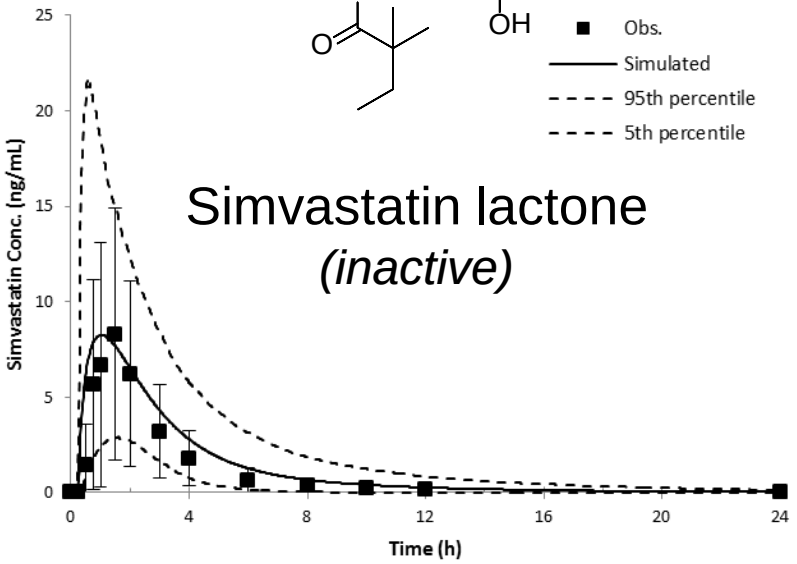
*Lin W. et al., (2017) J. Pharm Sci, In press*

# Qualification of simvastatin and simvastatin acid-linked PBPK model

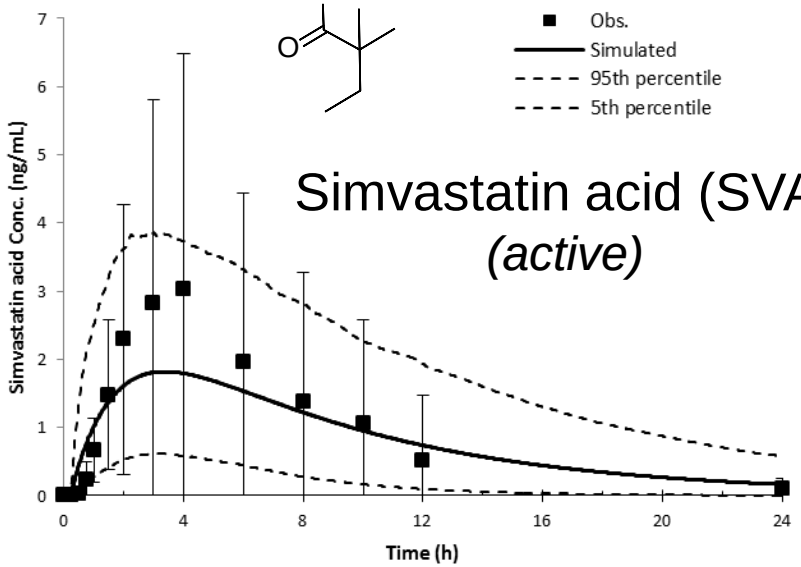


**Paraoxonases, Carboxylesterases**






Simvastatin lactone
*(inactive)*




Simvastatin acid (SVA)
*(active)*

| Simvastatin/LCZ696 | SVA: AUC Ratio | | SVA: Cmax Ratio | |
|---|---|---|---|---|
| | Predicted | Observed | Predicted | Observed |
| SV dosed 2 h after LCZ696 | 1.06 | 1.01 | 1.02 | 1.16 |
| SV dosed 1 h after LCZ696 | 1.08 | 0.90 | 1.04 | 0.96 |
| Co-administration | 1.10 | 0.89 | 1.09 | 0.87 |

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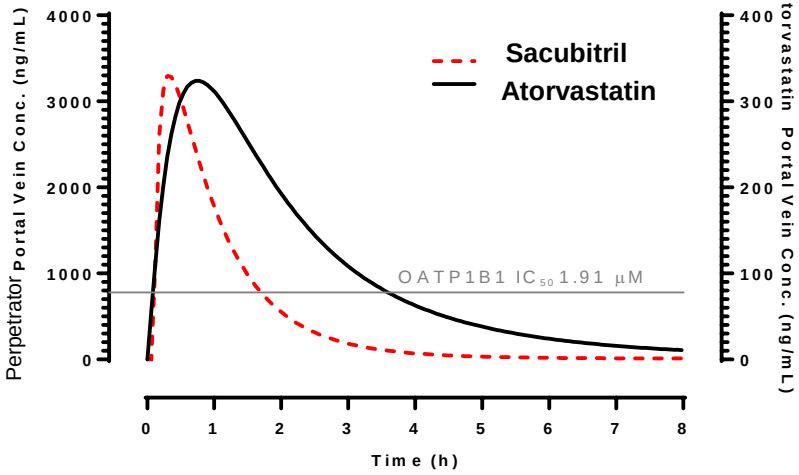
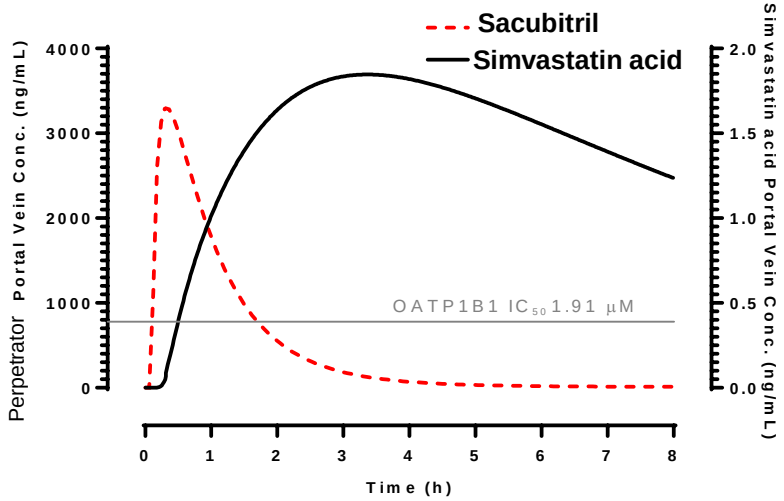
*Lin W. et al., (2017) J. Pharm Sci, In press*

# Why was there no DDI observed?

## Sacubitril: short Tmax, rapidly cleared via hydrolysis




<u>Rapidly absorbed statin</u> (Tmax: <1.5 h)

- Cmax increase max 2-fold
- AUC increase < 1.5-fold

<u>Slowly absorbed statin</u> (Tmax: >1.5 h)

- No meaningful effect on PK with sacubitril

Static DDI predictions: do not take into consideration Tmax, Ft, $P_{app,passive}$

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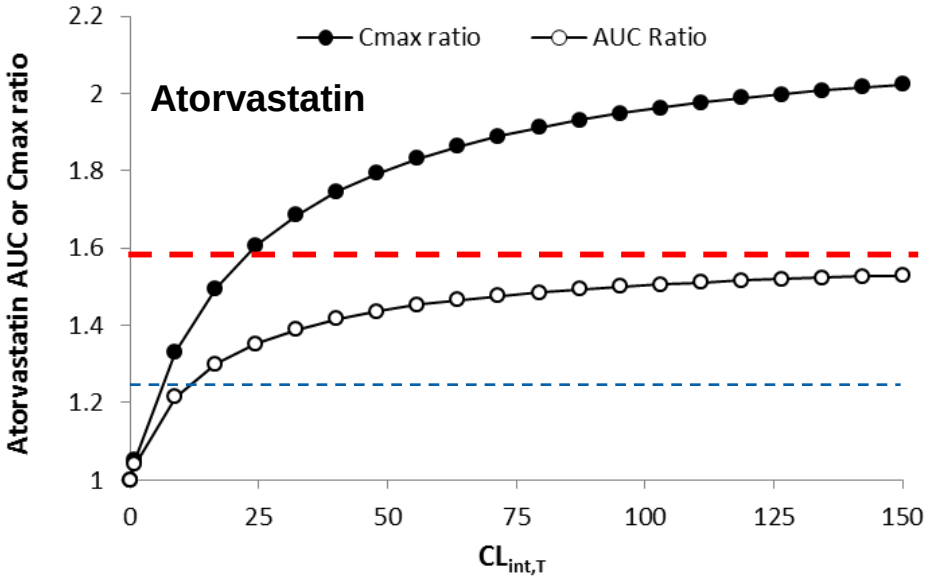
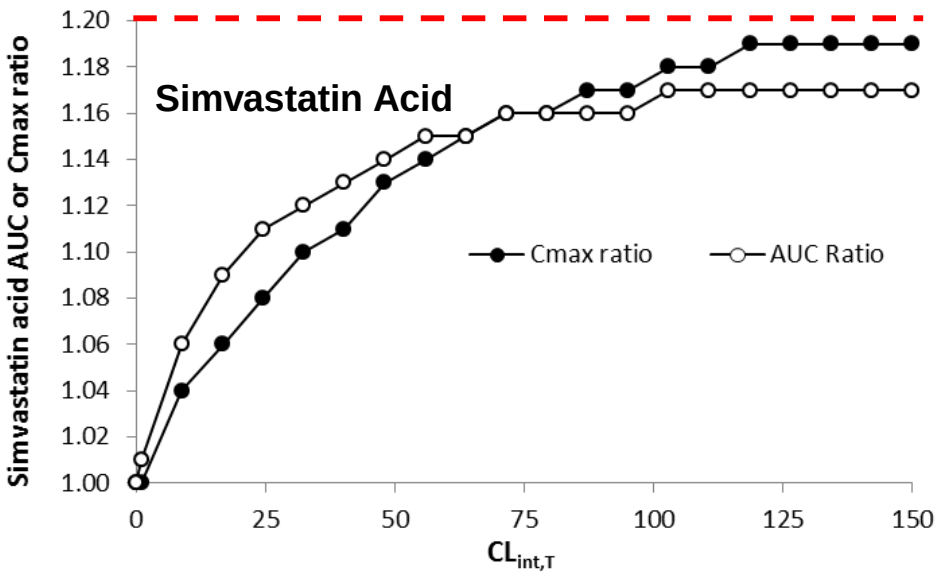
*Lin W. et al., (2017) J. Pharm Sci, In press*

# Hepatic OATP uptake clearance/statin PK parameter sensitivity analysis




- Sacubitril has the potential to act as a short-lived perpetrator of OATP-mediated DDIs
- Maximal increases of approximately 1.2 fold in the exposure of statins that exhibit a delayed Tmax are anticipated (e.g. simvastatin/lovastatin acid, rosuvastatin)
- Maximum change in exposure ~1.6-fold is anticipated with statins that exhibit Tmax values that coincide with that of sacubitril (e.g. atorvastatin, pitavastatin, pravastatin)

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*Lin W. et al., (2017) J. Pharm Sci, In press*

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