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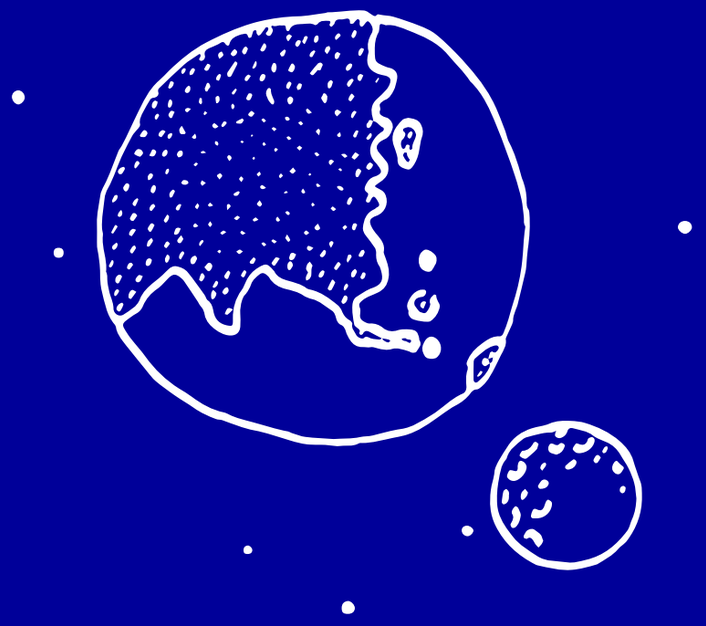
Deciphering the Clinical DDI Between Atazanavir and Rosuvastatin

Cyprotex, January 2024

Agenda

1. Introduction to drug-drug interactions
2. Introduction for the DDI between rosuvastatin and protease inhibitors
3. DDI predictions
4. Summary



Drug-Drug Interactions

Introduction

- Polypharmacy
  - Aging population and co-morbidities
    - 1 in 2 patients over 65 years old are prescribed ≥ 5 drugs
    - Polypharmacy common in Type 2 diabetes, heart failure and depression
  - Combination therapies in conditions such as HIV and cancer

- DDI occur when one drug affects the pharmacokinetics or pharmacodynamics of a co-administered drug
  - Impact on blood and tissue concentrations of drug or metabolite(s)
  - Alter safety and efficacy profile

- Pharmacokinetic DDI are mediated via mechanistic changes in the processes of absorption, distribution, metabolism and elimination (ADME) of the victim drug by another drug when they are co-administered

Victim: The drug (substrate) whose exposure (AUC) may or may not be changed by another drug

Perpetrator: The drug that causes an effect on the exposure of the victim drug by inhibiting / inducing enzymes or transporters

Drug-Drug Interactions

Transporters

- Evaluating the DDI potential of an investigational drug involves:
  - Identifying principal routes of drug elimination
  - Estimating contribution of transporters to drug disposition
  - Characterising effect of drug on transporters
- Along with clinical PK data, *in vitro* DDI data provides mechanistic information that can inform the need for and design of potential clinical studies

Key questions to answer

- **Victim:**
  - Is there potential for my drug to be a victim of a DDI?
  - What transporters are involved in the disposition of the drug?
- **Perpetrator:**
  - Does my drug inhibit transporters demonstrated to be critical in the disposition of other drugs and if so which “victim” drugs?
  - Could my drug perpetrate a DDI?

Understanding the interplay and risk associated with co-medications and DDI’s is critical for ensuring patient safety and achieving market approval

Human Immunodeficiency Virus (HIV)

Since the 1980's >85 million people have been infected with HIV: >40 million people have died from AIDS[1]

Infection/Disease

- Viral infection that is transmitted through the transfer of infected bodily fluids such as blood, salvia or via sexual contact
- HIV slowly destroys the immune system and increases the risk of other infections/diseases
  - Dislipidemia is a common comorbidity in patients with HIV and therefore the HMG-CoA reductase inhibitor rosuvastatin is a common co-medication
- Progression of the HIV infection can lead to acquired immune deficiency syndrome (AIDS)

Treatment

- No cure - but several marketed drugs are able to slow the progression of the disease
- Main therapy strategy used is Highly Active AntiRetroviral Therapy (HAART) – not curative and requires lifelong medication
  - Customised combination therapy
  - Improve quality of life
  - Reduce viral load → reduced transmission

1 World Health Organization (2023) https://www.who.int/data/gho/data/themes/hiv-aids (accessed December 2023)

Protease Inhibitors

- One of the main classes of HAART agents are protease inhibitors (PI)
- PIs are analogues of substrates of the HIV aspartyl protease enzyme
  - Aspartyl protease enzyme is required for the processing of viral proteins.
  - Once bound to the protease active site the PI inhibits further enzyme activity and proteolytic cleavage resulting in a lack of viral maturation.
    → Viral virion formation is ceased, instead forming non-infections virions.
- First marketed PI was saquinavir in 1995 followed by ritonavir in 1996 (first generation)
  - Second generation PIs with improved properties were developed enabling combination therapy alongside ritonavir
  - Atazanavir (2003) was the first PI to be dosed once daily increasing patient compliance
- Commonly prescribed protease inhibitors used in HAART include: atazanavir, darunavir and indinavir

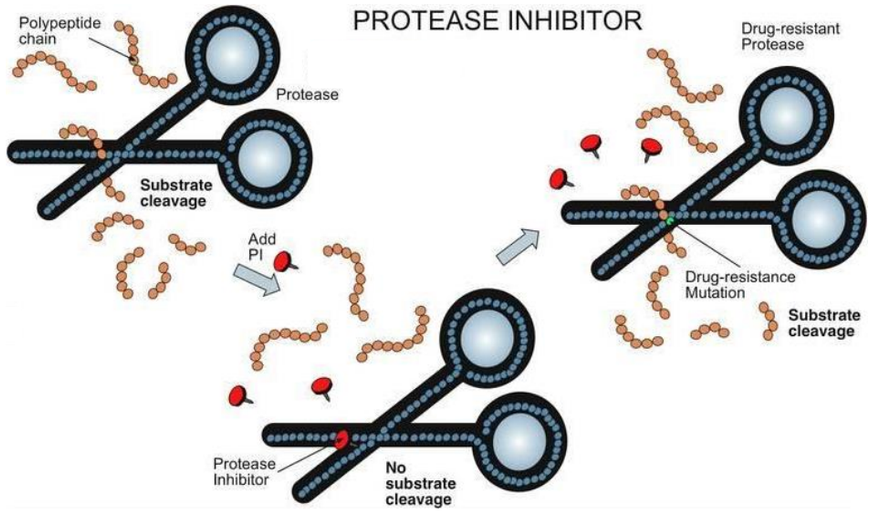


Figure 1: *Protease inhibitor mechanism of action*[1]

1 Ghosh AK, Osswald HL, Prato G. Recent Progress in the Development of HIV-1 Protease Inhibitors for the Treatment of HIV/AIDS. J Med Chem. 2016 Jun 9;59(11):5172-208. doi: 10.1021/acs.jmedchem.5b01697. Epub 2016 Jan 22. PMID: 26799988; PMCID: PMC5598487.

Rosuvastatin

- Patients infected with HIV are at an increased risk from further conditions, a common comorbidity is dyslipidaemia (24% of patients)[1]
- Rosuvastatin is a statin used to manage lipid levels by inhibiting production of cholesterol in the liver – more effective in managing lipid levels in HIV patients than other statins[2] → therefore it is the most commonly prescribed statin in this patient population
- DDI's have been reported resulting in myotoxicities due to elevated plasma levels of statin
- Clinical data has shown a 3-fold increase in exposure of rosuvastatin when co-administered with protease inhibitors[3]
- Understanding this interaction and identifying the critical disposition pathways of rosuvastatin will help mitigate the DDI and myotoxicity risk

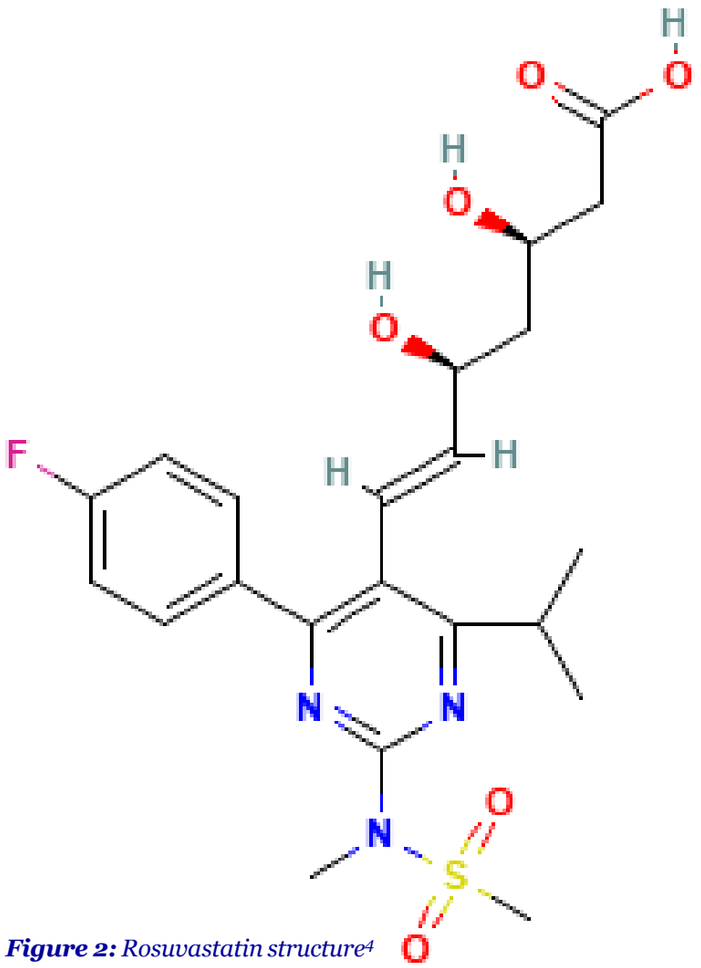


Figure 2: *Rosuvastatin structure*[4]

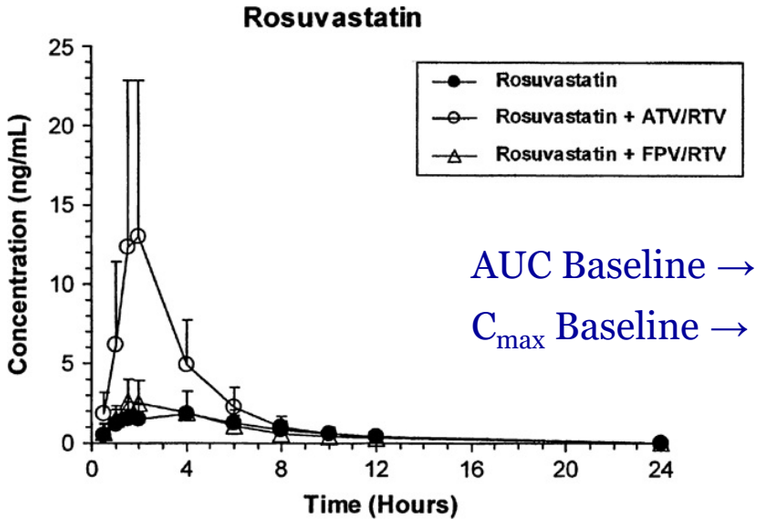
1 Elsby R, et al. (2023). Mechanistic *in vitro* studies indicate that the clinical drug-drug interactions between protease inhibitors and rosuvastatin are driven by inhibition of intestinal BCRP and hepatic OATP1B1 with minimal contribution from OATP1B3, NTCP and OAT3. Pharmacol Res Perspect. 2023 Apr;11(2):e01060
2 Lee D. HIV: how to manage dyslipidaemia in HIV. Drugs Context. 2022 Mar 1;11:2021-8-7. doi: 10.7573/dic.2021-8-7. PMID: 35310301; PMCID: PMC8903877.
3 Busti A et al. Effects of Atazanavir/Ritonavir or Fosamprenavir/Ritonavir on the Pharmacokinetics of Rosuvastatin. Journal of Cardiovascular Pharmacology 51(6):p 605-610, June 2008.
4 National Center for Biotechnology Information. PubChem Compound Summary for CID 446157, Rosuvastatin. https://pubchem.ncbi.nlm.nih.gov/compound/Rosuvastatin. Accessed Jan. 9, 2024.

Rosuvastatin & Atazanavir DDI

- Subjects dosed with 10mg of rosuvastatin – blood samples taken up to 24 hrs after dosing
- 6 day wash out period
- Day 7 – Day 14 atazanavir / ritonavir 300mg / 100mg was administered each morning
- Subjects dosed with 10mg of rosuvastatin on day 14 – blood samples taken up to 24 hrs after dosing

Parameter	Rosuvastatin* (baseline)	Rosuvastatin + ATV/RTV
Rosuvastatin		
AUC_{0-24} (ng*h/mL)	14.0 ± 9.9	43.8 ± 27.9
C_{max} (ng/mL)	1.90 ± 1.48	13.3 ± 9.7
T_{max} (h)	2.91 ± 1.20	1.75 ± 0.27

Table 1: *Pharmacokinetic Parameters (Mean ± SD) of Rosuvastatin when dose alone or in combination*



AUC Baseline → ATV/RTV ↑ 3.1 fold [3.0-3.9]

C_{max} Baseline → ATV/RTV ↑ 7 fold [6.8-8.6]

Figure 3: *Plasma concentration-time profile for rosuvastatin alone or co-dosed*

Co-administration of rosuvastatin and atazanavir/ritonavir results in a clinically significant DDI

1 Busti A et al. Effects of Atazanavir/Ritonavir or Fosamprenavir/Ritonavir on the Pharmacokinetics of Rosuvastatin. Journal of Cardiovascular Pharmacology 51(6):p 605-610, June 2008.

Rosuvastatin Disposition Pathway

- Oral administration of rosuvastatin is 50% absorbed
  - BCRP limiting absorption by 50% (f_e = 0.5)
- Once in the hepatic portal vein and at the inlet to the liver it is taken up into hepatocytes by a process which relies upon SLC uptake transporters for gaining entry to the liver (site of action)
- Rosuvastatin is a substrate of OATP1B1, OATP1B3 and NTCP, these are required to different extents for hepatic uptake clearance (hepatic extraction ratio of 0.72)
  - 97% active uptake
- Rosuvastatin is also actively renally cleared by OAT3 with 90% of uptake into the renal proximal tubule being due to transporter activity.

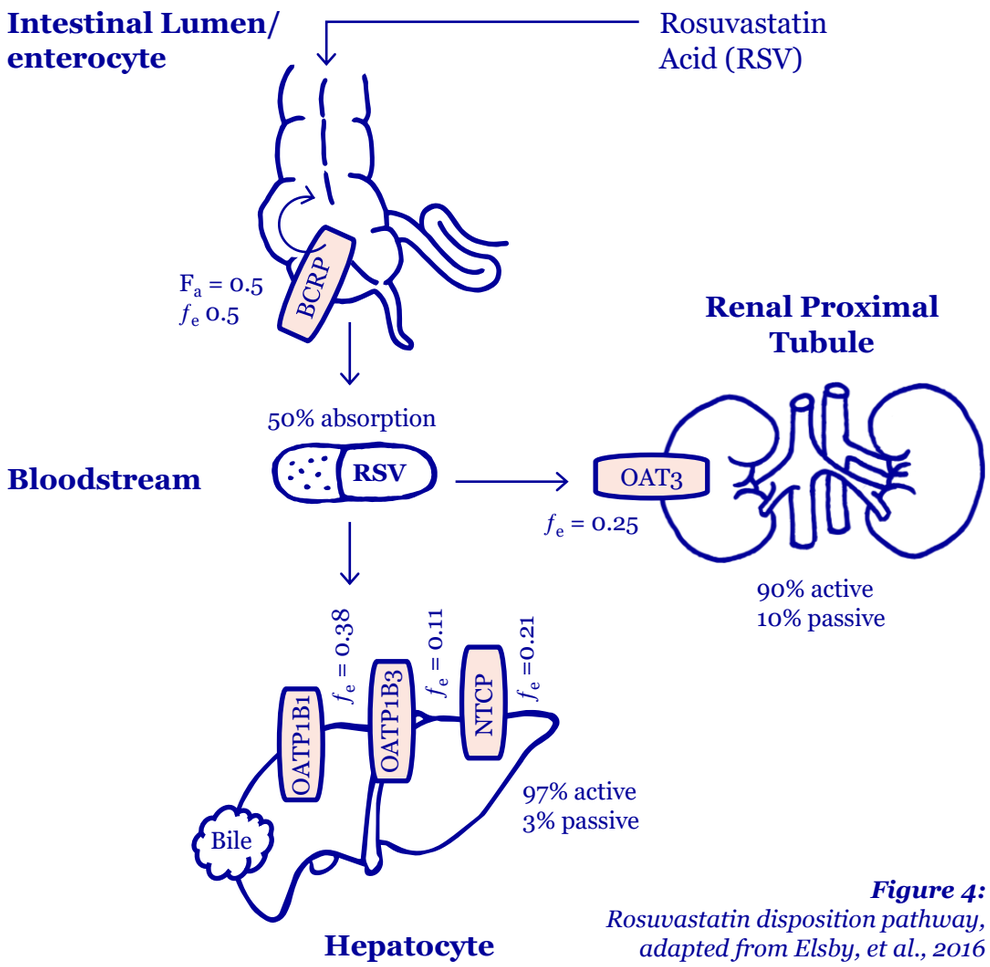


Figure 4:
Rosuvastatin disposition pathway, adapted from Elsby, et al., 2016

Elsby R, et al. (2016) Solitary Inhibition of the Breast Cancer Resistance Protein Efflux Transporter Results in a Clinically Significant Drug-Drug Interaction with Rosuvastatin by Causing up to a 2-Fold Increase in Statin Exposure. Drug Metab Dispos. 44(3):398-408.

Quantitative Tools – Application of the Rowland Matin Equation

Estimation 1

Adapted Rowland Matin mechanistic static equation and its derivatives can be used to quantitatively predict the extent of AUC changes of a victim drug due to DDI in the clinic

1. Maximum theoretical AUC change if an individual pathway is fully inhibited:
   Mechanistic theoretical maximum equation

Transporter		f_e	Fold Δ
OATP1B1[1]	Hepatic	0.38	1.61
OATP1B3	Hepatic	0.11	1.12
NTCP	Hepatic	0.21	1.27
BCRP[1]	Intestinal	0.5	2.0
OAT3	Renal	0.25	1.3

Table 2: *f_e values derived by Elsby (2012) and the subsequent maximal theoretical fold change in rosuvastatin AUC*

$$\textbf{Fold } \Delta = \frac{1}{1 - f_e}$$

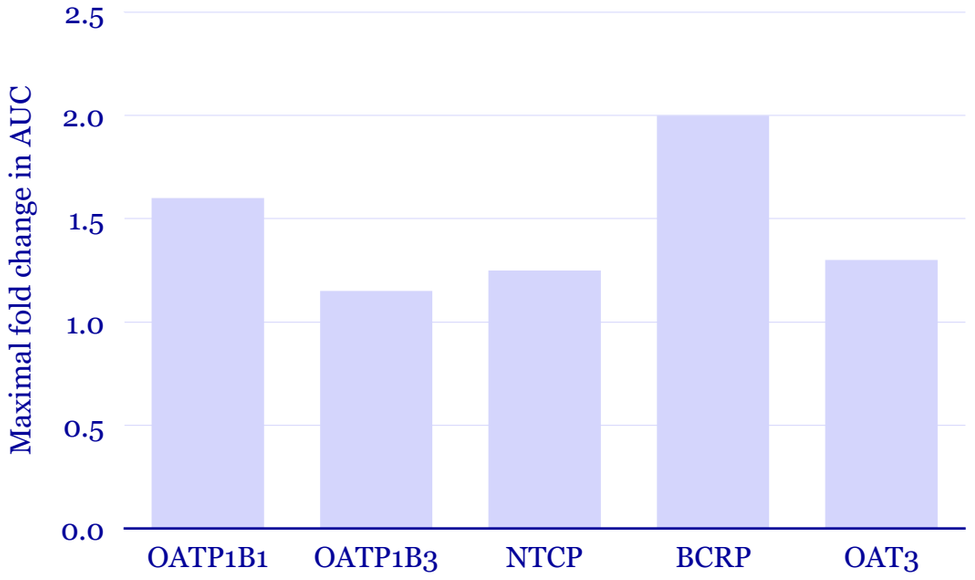


Figure 4: *Maximum fold change in AUC of Rosuvastatin assuming complete inhibition of individual transporters*

1 Critical pathways of rosuvastatin are BCRP and OATP1B1

Elsby R, Hilgendorf C, Fenner K. (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther.;92(5):584-98

Quantitative Prediction of Rosuvastatin-Atazanavir DDI

Estimation 1 continued

1. To decipher which pathways may be playing a crucial role in the rosuvastatin-atazanavir DDI the basic Rowland Matin equation can be applied, incorporating the f_e value only.

AUCR

$2.0_{(BCRP)} \times 1.61_{(OATP1B1)} = 3.22$

Assumptions

- Transporter is 100% inhibited by atazanavir
- Only 2 pathways of significance

- Mathematically close to the observed DDI, however not representative of a true clinical scenario based on the assumptions above
- The disposition pathway of rosuvastatin has been determined and involves multiple hepatic transporters to achieve the overall f_e of 0.7 …

Quantitative Prediction Tools

Adapted Rowland Matin mechanistic static equation and its derivatives can be used to quantitatively predict the extent of AUC changes of a victim drug due to DDI in the clinic

1. Maximum theoretical AUC change if an individual pathway is fully inhibited:
   Mechanistic theoretical maximum equation

$$\text{Fold } \Delta = \frac{1}{1-f_e}$$

2. Incorporating *in vitro* and *in vivo* parameters for an individual pathway:
   Mechanistic static equation

$$\text{Fold } \Delta = \frac{1}{\frac{f_e}{(1+\frac{[I]}{K_i})} + (1 - fe)}$$

3. Incorporating *in vitro* and *in vivo* parameters for multiple pathways:
   Mechanistic static equation

$$\text{Fold } \Delta = \frac{1}{\left(\frac{f_e}{1+\frac{[I]}{K_i}}\right) + \left(\frac{f_e}{1+\frac{[I]}{K_i}}\right) + \left(\frac{f_e}{1+\frac{[I]}{K_i}}\right) + (1 - f_{e\,total})}$$

Previously Published Predictions for the Clinical DDI

Prediction 1

1. Predictions of rosuvastatin AUCR have been made integrating solely the critical pathways of BCRP and OATP1B's: Rowland Matin equation, incorporating literature K_i values

Table 4 Inhibitory properties and pharmacokinetic parameters of coadministered drugs that have caused drug–drug interactions with statins

Statin	Perpetrator drug	Dose (mg)	MW	$[I_2]$ (μmol/l)	IC_{50} or K_i values (μmol/l)						f_u	C_{max}, total (μmol/l)	$I_{inlet\ max}$, unbound (μmol/l)	Reference in Supplementary Data online
					BCRP	OATP1B1	OATP1B3	OAT3	CYP3A4	CYP2C9				
	Atazanavir	300	704.9	1,702	69.1	1.5	2.0	[b]	NR	NR	0.14	8.68	5.19	102, 103, 112

Table 6 Predicted vs. observed fold increases in pitavastatin, pravastatin, and rosuvastatin AUC for the known statin DDIs shown in Table 3

Statin	Perpetrator drug	Predicted fold increase in AUC due to inhibition of composite pathways			Overall predicted fold increase in AUC	Clinically observed fold increase in AUC
			OATP1B(1 and 3)			
		BCRP (intestine)	Active uptake (OATP1B1:NTCP:OATP1B3) (f_e = 0.38:0.21:0.11 = 0.7)	OAT3		
	Atazanavir/ ritonavir	2.0 [25]	1.6 (OATP1B) (3.5)	NA	3.2	3.1

- Complete inhibition of BCRP and inhibition of OATP1B
- Estimation of clinical observation based on number of assumptions

Assumptions

- Max intestinal luminal conc used (I_2 now termed I_{gut}) for BCRP
- Complete inhibition of BCRP obtained when I_2/K_i >10, therefore AUCR=2.0
- Combined OATP1B f_e (0.38+0.11=0.49)
- Inhibitory potency of OATPs is identical at 1B1 and 1B3

$$\text{Fold } \Delta = \frac{1}{\frac{f_e}{(1+\frac{[I]}{K_i})} + (1 - fe)}$$

AUCR

3.2 (predicted) vs 3.1 (clinical)

Elsby R, Hilgendorf C, Fenner K. (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther.;92(5):584-98

Previously Published Predictions for the Clinical DDI

Prediction 2

2. When the assumption was made that atazanavir was an inhibitor of the 3 hepatic clearance routes, (OATP1B1, OATP1B3 and NTCP giving the combined f_e of 0.7) did the prediction in AUC change of rosuvastatin fall in line with the clinical data

Victim drug	Perpetrator drug	I_g (µM)	$I_{in\ max}$ (µM)	IC_{50} or K_i values (µM)	
				BCRP	OATP1B1
Rosuvastatin	Atazanavir	142	4.9	69.1	1.5

Victim drug	Perpetrator drug	AUCR		
		BCRP	Hepatic (OATP1B1, OATP1B3 & NTCP)	BCRP + Hepatic
Rosuvastatin	Atazanavir	1.51	2.19	3.3

- Utilises literature K_i values, $I_{gut\ max}$ used – more biologically relevant
- BCRP pathway is not fully inhibited, and potentially the combined hepatic pathways are implicated to a greater extent than previously predicted.
- Over prediction of the AUCR using assumptions

Assumptions

- Full hepatic f_e used (0.38+0.11+0.21)
- Inhibition (K_i) of OATP1B3 and NTCP were identical to OATP1B1

$$\text{Fold } \Delta = \frac{1}{\frac{f_e}{(1+\frac{[I]}{K_i})} + (1 - fe)}$$

AUCR

3.25 (predicted) vs 3.1 (clinical)

Note: Using data and values from the 2012 paper but using the Igut max not Igut (I2)

Elsby R, Hilgendorf C, Fenner K. (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther.;92(5):584-98

Improving on Predictions of the Clinical DDI

Existing predictions used several assumptions to predict the AUCR of rosuvastatin when co-dosed with atazanavir, can these be improved further?

- Generate IC_{50} (K_i) values for all transporters that contribute to the critical disposition pathways of rosuvastatin
- Use more up to date *in vitro* inhibition methodologies to derive the most accurate IC_{50} value for predictions
  - Inclusion of atazanavir pre-incubation step (15 min) prior to co-incubation with probe substrate
  - Use of probe substrates demonstrated to be surrogates for the clinically relevant substrate (rosuvastatin)
    - (Estrone 3-sulfate for BCRP, Estradiol 17β -glucuronide for OATP1B1)

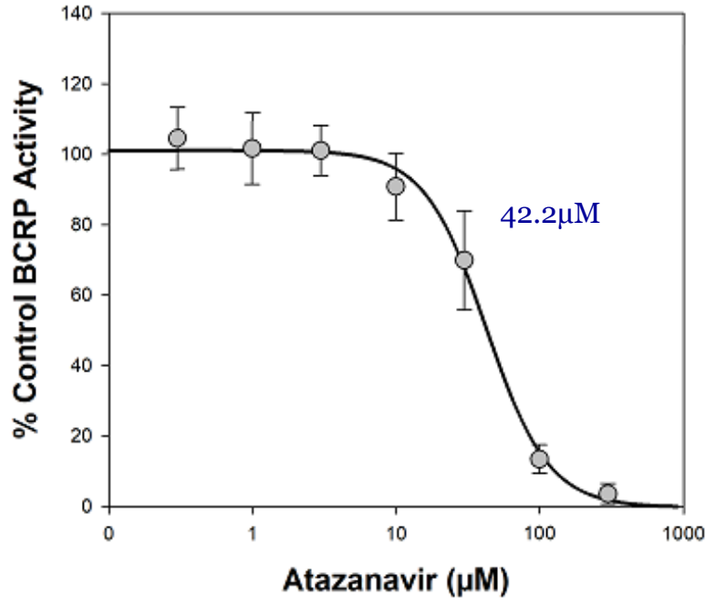
Do we still predict that the clinical AUCR change of 3.1 is attributed to inhibition of BCRP and all hepatic transporters, OR predict it is due to inhibition of BCRP and OATP1B1 only?

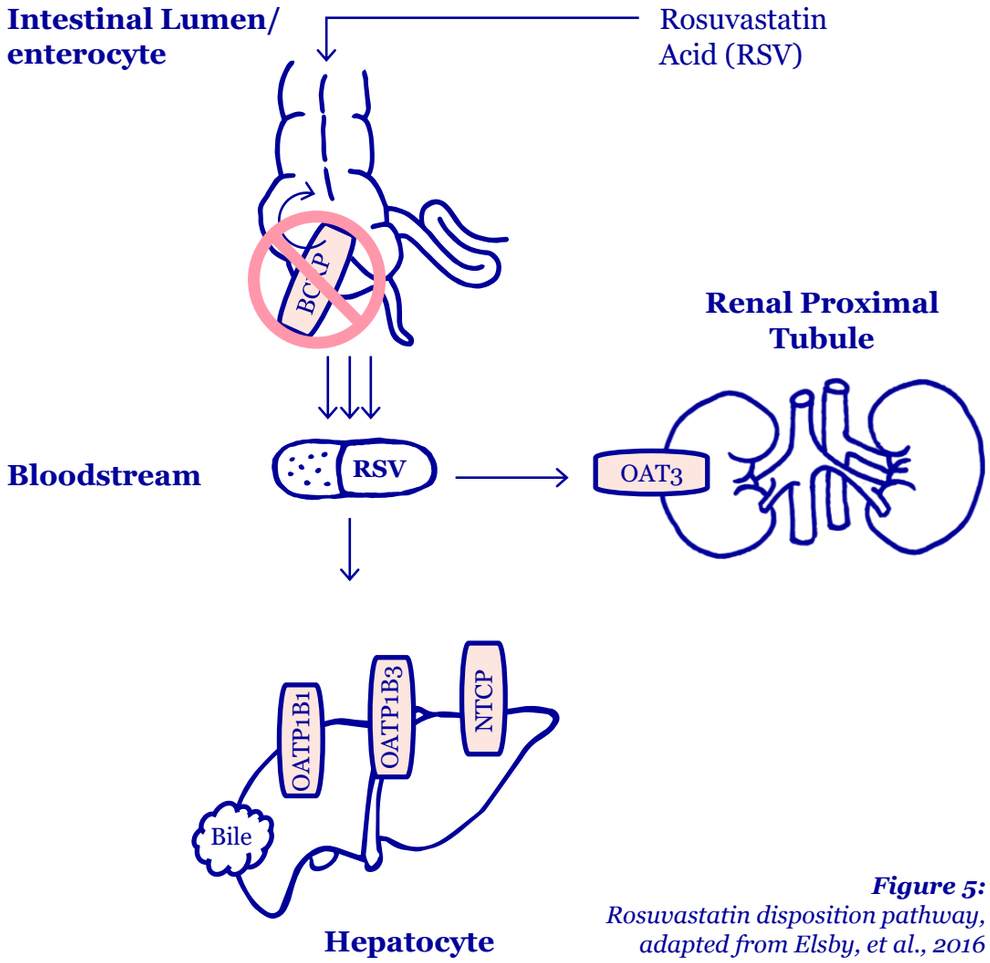
Impact of Atazanavir on Rosuvastatin Disposition

BCRP Inhibition

In vitro experiments showed BCRP transport of [^{3}H]-estrone 3-sulfate (surrogate for rosuvastatin) to be inhibited by atazanavir with an IC_{50} of 42.2 µM

Using the updated methodology, the determined potency has increased, decreasing the IC_{50} value from 69.1 µM





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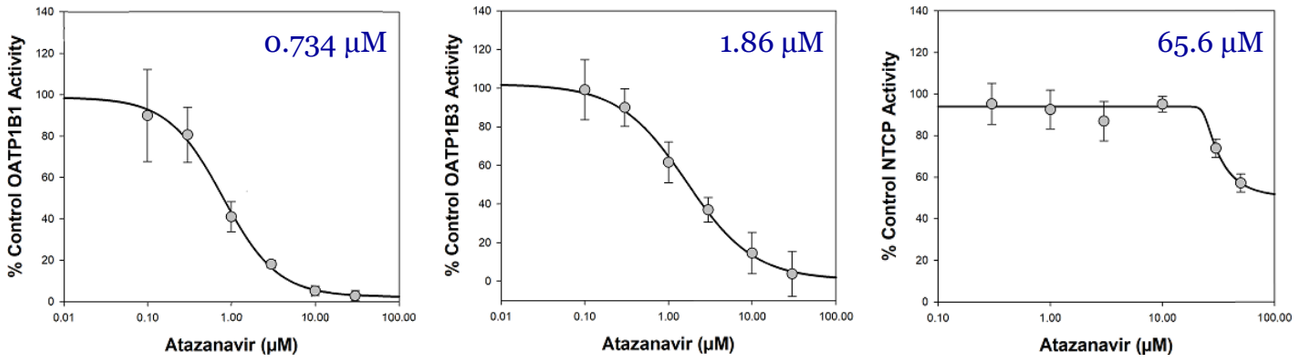
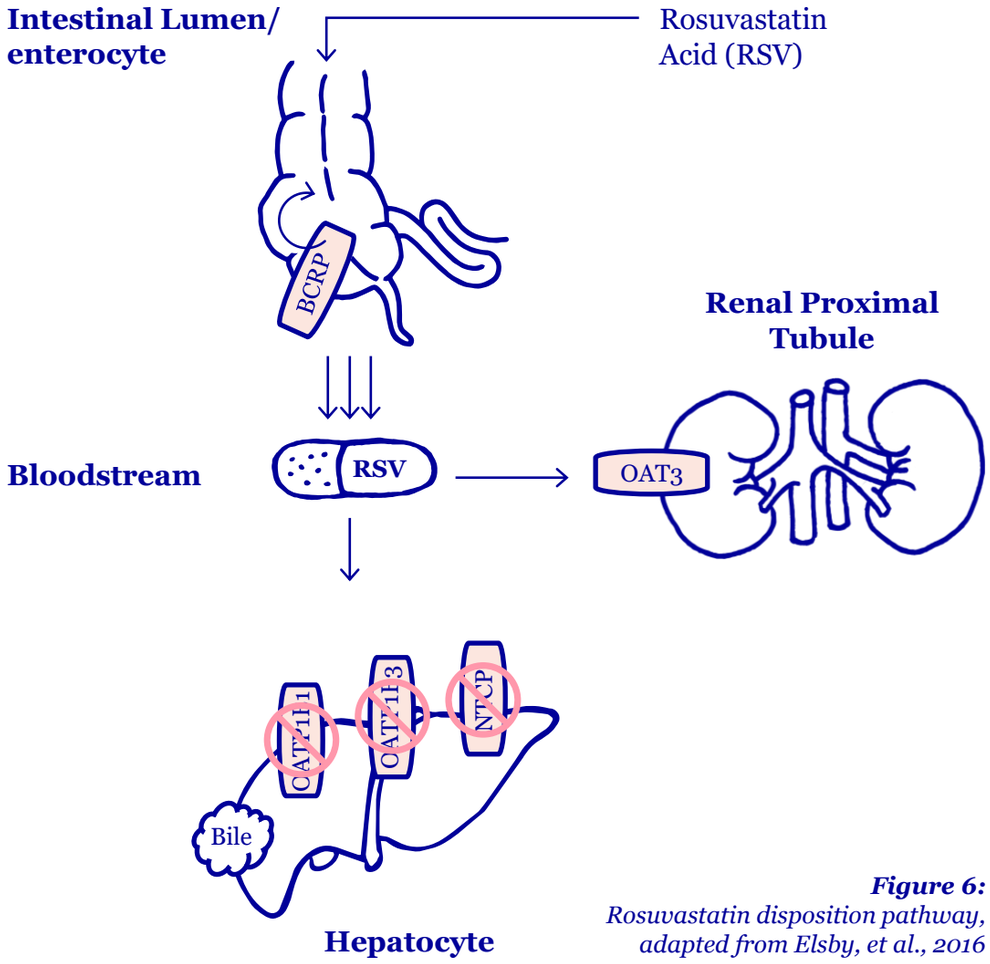
Impact of Atazanavir on Rosuvastatin Disposition

SLC Inhibition

In vitro experiments showed atazanavir to inhibit OATP1B1, OATP1B3 and NTCP mediated transport with IC_{50}'s of 0.734 µM, 1.86 µM and 65.6 µM respectively, but not against OAT3

IC_{50}'s using the updated *in vitro* methodology have decreased from the previously reported values of 1.5 and 2 µM for OATP1B1 and OATP1B3 respectively





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Rosuvastatin disposition pathway, adapted from Elsby, et al., 2016

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Quantitative Prediction: Application of Determined *In Vitro* Parameters

Prediction 3a

3a) Theoretical AUCR if an individual pathway is inhibited, or the combined AUCR for these four pathways

Transporter	f_e	K_i	Equation	AUCR	Overall AUCR
OATP1B1	0.38	0.734	$\frac{1}{\frac{f_e}{(1+\frac{[I]}{K_i})}+(1-fe)}$	1.49 [1.44-1.56]	2.43
BCRP	0.5	42.2		1.63 [1.55-1.73]	

[I] = [$I_{in,max,u}$], unbound maximum hepatic inlet concentration = 4.9 µM, or [I_g], maximal enterocyte concentration = 142 µM; K_i = reversible inhibition constant (for transporters; this is equivalent to IC_{50} if [probe substrate] <<<< K_m in assay); [ ] numbers in square brackets are the calculated predicted AUCR range using the upper and lower 95% confidence intervals determined for each inhibitory parameter

AUCR BCRP & OATP1B1 only – $2.43_{(predicted)}$ vs $3.1_{(clinical)}$

Neither OATP1B1 nor BCRP are fully inhibited, and the combined effect on rosuvastatin AUCR is underpredicted.

Quantitative Prediction: Application of Determined *In Vitro* Parameters

Prediction 3b

3b) Theoretical AUCR if an individual pathway is inhibited, or the combined AUCR for these four pathways

Transporter	f_e	K_i	Equation	AUCR	Equation	AUCR	Overall AUCR
OATP1B1	0.38	0.734	$\frac{1}{\frac{f_e}{(1+\frac{[I]}{K_i})}+(1-fe)}$	1.49 [1.44-1.56]	$\frac{1}{\left(\frac{f_e}{1+\frac{[I]}{K_i}}\right)_{(Trspt1)}+\left(\frac{f_e}{1+\frac{[I]}{K_i}}\right)_{(Trspt2)}+\left(\frac{f_e}{1+\frac{[I]}{K_i}}\right)_{(Trspt3)}+(1-f_{e\,total})}$	1.74	2.84 [2.53-3.32]
OATP1B3	0.11	1.86		1.09 [1.07-1.11]			
NTCP	0.21	65.6		1.01 [1.01-1.02]			
BCRP	0.5	42.2		1.63 [1.55-1.73]	$\frac{1}{\left(\frac{f_e}{1+\frac{[I_g]}{K_i}}\right)+(1-fe)}$	1.63	

[I] = [$I_{in,max,u}$], unbound maximum hepatic inlet concentration = 4.9 µM, or [I_g], maximal enterocyte concentration = 142 µM; K_i = reversible inhibition constant (for transporters; this is equivalent to IC_{50} if [probe substrate] <<<< K_m in assay); [ ] numbers in square brackets are the calculated predicted AUCR range using the upper and lower 95% confidence intervals determined for each inhibitory parameter

AUCR $2.84_{(predicted)}$ vs $3.1_{(clinical)}$

Combined effect of all 4 transporters improves the predicted AUCR, within 30% of the clinical observation

Comparison of Predictions for the Rosuvastatin-Atazanavir DDI

- Using the various prediction tools and associated assumptions the fold change in AUC ranges from 2.43 to 3.25 compared to the clinically observed value of 3.1
- Mechanistic theoretical maximum equation in the absence of $[I]/K_i$ can mathematically predict the AUCR of rosuvastatin when dosed with atazanavir, **HOWEVER** it is:
  - Not biologically relevant
  - Not perpetrator/concentration dependent – therefore not likely to be correct, rather simply coincidence
- The most biologically relevant approach to use for AUCR prediction is to incorporate all the pathways contributing to the overall fraction excreted value of any given critical disposition route

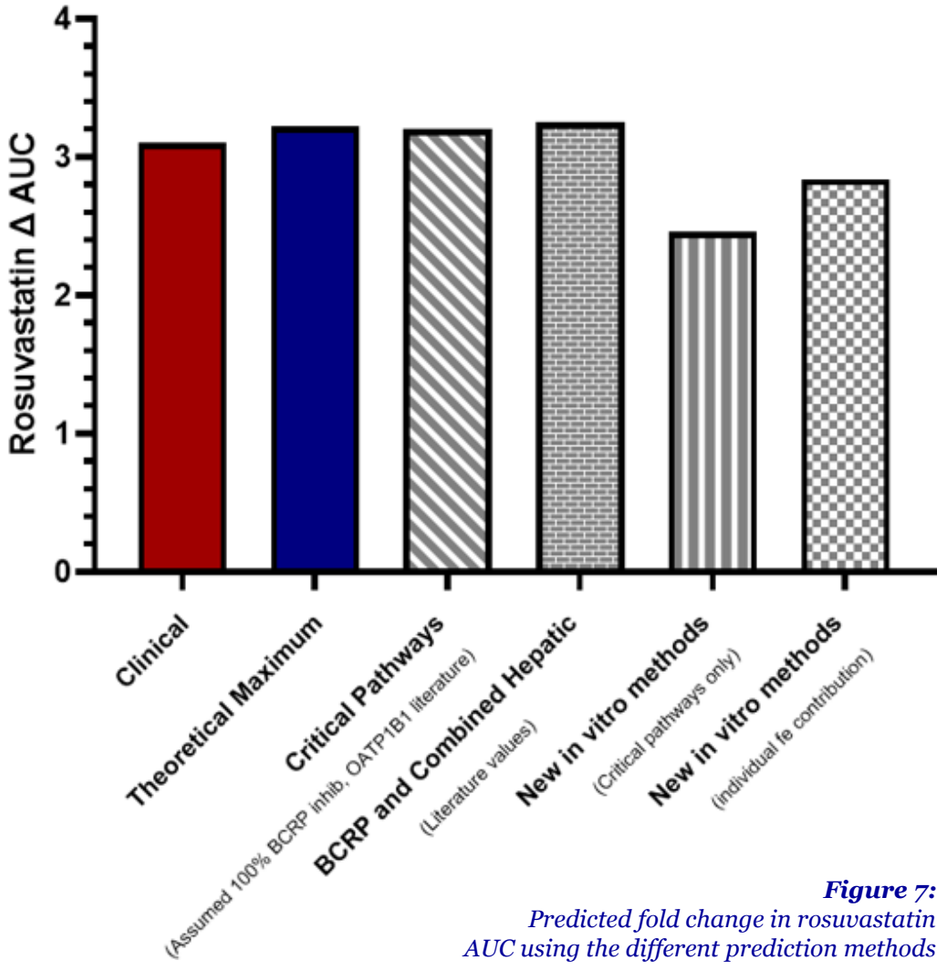

Figure 7:
Predicted fold change in rosuvastatin AUC using the different prediction methods

Accuracy of Predictions

Predictive tool	Predicted AUCR	Accuracy of prediction (%) [95% CI]
Mechanistic theoretical maximum equation for f_e (BCRP + OATP1B1)	3.22	+12 [22-68]
BCRP and combined OATP from literature *in vitro* data ([gut] = lumen)	3.2	+ 10 [20-70]
BCRP and hepatic (assumed) from literature *in vitro* data + physiologically relevant [I_g]	3.25	+ 15 [25-65]
New *in vitro* parameter data for BCRP & OATP1B1 only (inc pre-incubation)	2.43	- 67 [57-147]
New *in vitro* parameter data for BCRP and all hepatic (inc pre-incubation)	2.84	- 26 [16-106]
Clinical AUCR	**3.1** [3-3.9] (210% AUC increase due to atazanavir)	

Mechanistic static model for 28 statin DDIs (6 statin victim drugs)

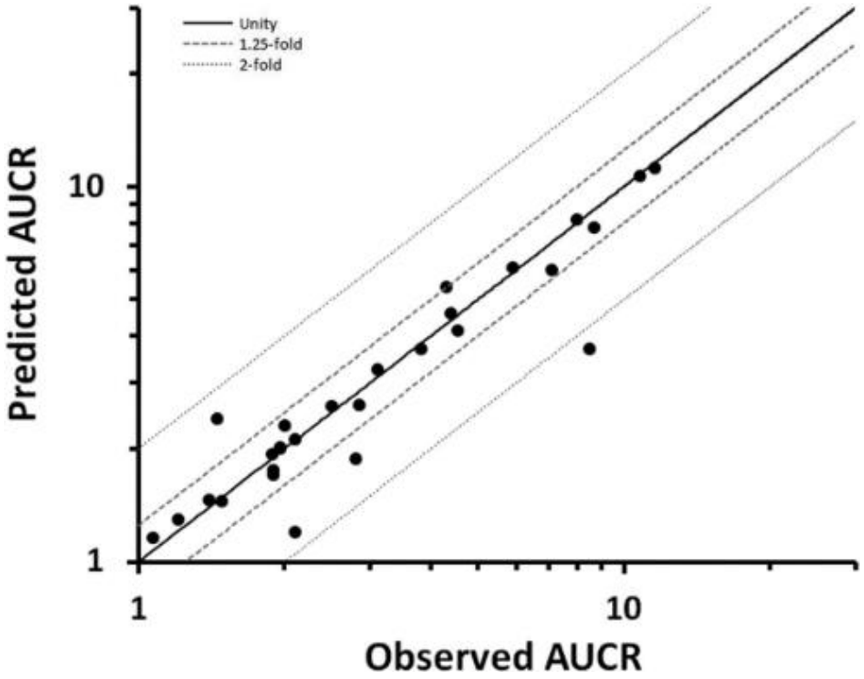

Figure 8: *Predicted AUCR of 6 statin drugs and their perpetrators (28 DDI's)*

Accuracy of the predictions over time has changed, becoming more biologically relevant as the predictive tools develop

1 Elsby R., et al. (2022) Studying the right transporter at the right time: an *in vitro* strategy for assessing drug-drug interaction risk during drug discovery and development, Expert Opinion on Drug Metabolism & Toxicology, 18:10, 619-655,

Summary of Predictions

	Method	AUCR Prediction	Assumptions	Calculations Variances	Reference
Estimate 1	Combination of individual f_e	**3.22**	Transporters are 100% inhibited Only 2 pathways at play	f_e only	
Prediction 1	Combined OATP f_e	**3.2**	Complete inhibition when $I_2/K_i > 10$	Max luminal conc used (I_2) [dose/250mL] for BCRP – 1702µM	Elsby. R et al., (2012)
			Combined OATP f_e (0.38+0.11)	Hepatic blood flow 1500mL/min	
	Literature values		Inhibitory potency of OATPs consistent across isoforms	Unbound hepatic inlet conc ($I_{in\ max}$) 5.19 literature value	
			F_a, F_g = 1, k_a = 0.1		
Prediction 2	Combined hepatic f_e (all SLC)	**3.25**	Full hepatic f_e used (0.38+0.11+0.21)	I_g (max enteroctye conc) 142µM	Elsby. R et al., (2022)
	Updated parameters		Inhibition (K_i) of OATP1B3 and NTCP were similar to OATP1B1	Hepatic blood flow 1614mL/min → Unbound hepatic inlet conc ($I_{in\ max}$) 4.9 µM	
	Literature values		F_a, F_g = 1, k_a = 0.1		
Prediction 3a	Improved *in vitro* method	**2.43**	Only 2 pathways at play	Updated parameters (I_g , $I_{in\ max}$, Q_h)	Elsby. R et al., (2023)
	In vitro parameters			*In vitro* data incorporated	
	Major pathways only		F_a, F_g = 1, k_a = 0.1		
Prediction 3b	Improved *in vitro* method *In vitro* parameters All pathways contributing to f_e	**2.84**	F_a, F_g = 1, k_a = 0.1		

1 Elsby R, Hilgendorf C, Fenner K. (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther.;92(5):584-98
2 Elsby R, et al. (2022) Studying the right transporter at the right time: an *in vitro* strategy for assessing drug-drug interaction risk during drug discovery and development, Expert Opinion on Drug Metabolism & Toxicology, 18:10, 619-655,
3 Elsby R, et al. (2023). Mechanistic *in vitro* studies indicate that the clinical drug-drug interactions between protease inhibitors and rosuvastatin are driven by inhibition of intestinal BCRP and hepatic OATP1B1 with minimal contribution from OATP1B3, NTCP and OAT3. Pharmacol Res Perspect. 2023 Apr;11(2):e01060

Rosuvastatin Drug Label

- Due to the observed clinical DDI interaction seen between protease inhibitors and rosuvastatin this has been incorporated into the drug label
- When administering this combination, the dosages of each drug must be considered to ensure a safe and efficacious dose is achieved for both counterparts

7.3 Protease Inhibitors

Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold *[see Table 3 – Clinical Pharmacology (12.3)]*. For these combinations the dose of CRESTOR should be limited to 10 mg. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir [*see Dosage and Administration* (2.5), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir [*see Dosage and Administration* (2) and *Drug Interactions* (7)].

Drug-Drug Interactions:

Cytochrome P450 3A4

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Table 4. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	Rosuvastatin		
	Dose (mg)*	Change in AUC**	Change in C_{max}**
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	↑ 7-fold†	↑11-fold†
Gemfibrozil 600 mg BID for 7 days	80 mg	↑ 1.9-fold†	↑ 2.2-fold†
Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 days	20 mg QD for 7 days	↑ 2-fold†	↑ 5-fold†
Atazanavir/ritonavir combination 300 mg/100 mg QD for 7 days	10 mg	↑ 3-fold†	↑ 7-fold†
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	↑ 26%	↑ 2-fold
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	↑ 8%	↑ 45%
Fenofibrate 67 mg TID for 7 days	10 mg	↑ 7%	↑21%
Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	 40 mg 40 mg	 ↓ 54%† ↓ 22%	 ↓ 50%† ↓ 16%
Erythromycin 500 mg QID for 7 days	80 mg	↓ 20%	↓ 31%
Ketoconazole 200 mg BID for 7 days	80 mg	↑ 2%	↓ 5%
Itraconazole 200 mg QD for 5 days	10 mg 80 mg	↑ 39% ↑ 28%	↑ 36% ↑ 15%
Fluconazole 200 mg QD for 11 days	80 mg	↑ 14%	↑ 9%

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Clinically significant [*see Dosage and Administration* (2) and *Warnings and Precautions* (5)]

1 AstraZeneca. Crestor [Package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s016lbl.pdf. Revised 2010. Accessed December 2023

Summary

1. Prediction methods have developed over time as the understanding of DDI and biological parameters improves
2. The correct *in vitro* parameters and the correct victim model (critical disposition route(s) and associated f_e values and assumptions) are required for mechanistic models for successful prediction
3. Rosuvastatin/atazanavir DDI is explained by mechanistic model incorporating all hepatic transporters and intestinal BCRP
4. Prediction of 2.84 ΔAUC is in line with the clinical observation of 3.1
5. *In vitro* assays are important for predicting DDI's and can help inform clinical trials

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QUESTIONS AND ANSWERS