CHANGES IN ACTIVITY OF HEPATIC TRANSPORTERS IN PATIENTS WITH RENAL IMPAIRMENT

Hepatocyte Transporter Network,
Les Diablerets, Switzerland

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INVENTING FOR LIFE

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Outline

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Disease-Associated Changes in Drug Transporters May Impact the Pharmacokinetics and/or Toxicity of Drugs: A White Paper From the International Transporter Consortium

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on behalf of the International Transporter Consortium

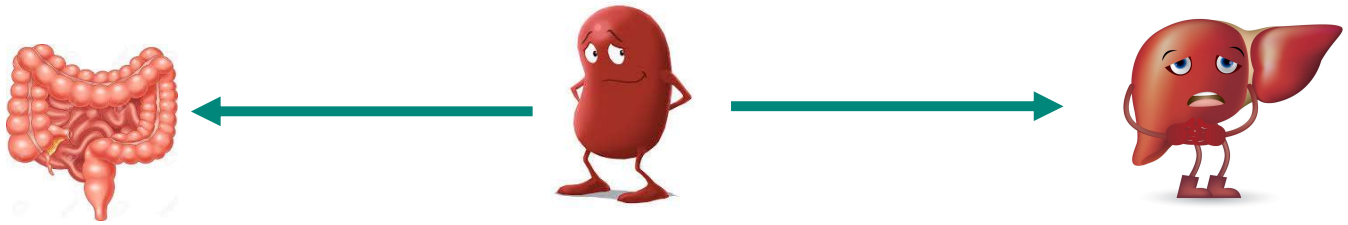
Focus for presentation today

- What is known about the effect of kidney disease on liver transporters?
- Microdose cocktail results
  - Effect of renal impairment (RI) on liver/intestine transporter substrates
  - Effects on endogenous biomarkers for liver transporters
- Conclusions

Impact of Chronic Kidney Disease (CKD) on Hepatic Enzymes and Transporters

	Clinical Impact
CYP3A4/5	No consistent impact
CYP2D6, CYP2C8	↓ clearance
CYP1A2, CYP2C9, CYP2C19	Minimal and variable
OATP1B	↓ uptake/clearance

Drug absorption:
Transporters?
Enzymes?

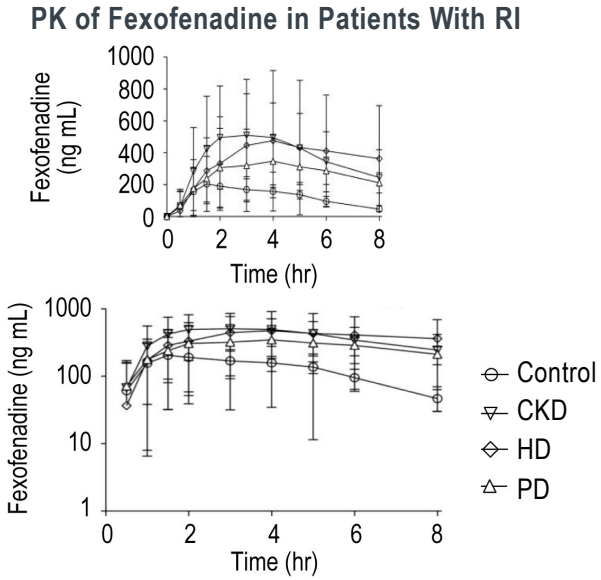


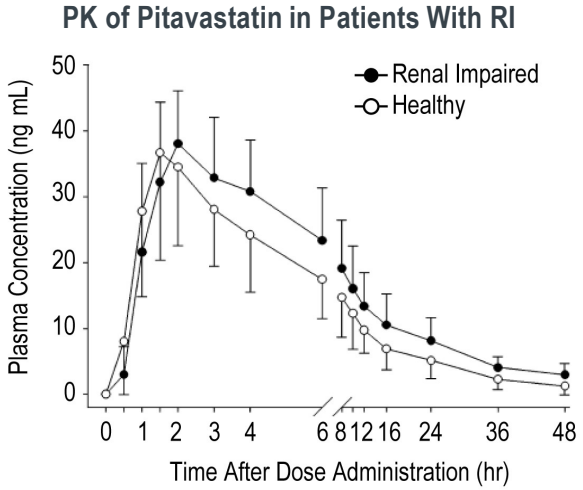
Clearance:
Transporters?
Enzymes?

Uremic Toxins
Inflammatory response
Changes in plasma protein binding
Changes in volume of distribution

Tan ML, et al. *Clin Pharmacol Ther.* 2019;105(3):719-729. Yoshida K, et al. *Clin Pharmacol Ther.* 2016;100(1):75-87.

Increased Exposure of Transporter Substrates Cleared Nonrenally in Patients with CKD





Disease State	Drug	Transporter/Enzyme	$AUC_{0\text{-last}}$ Patients	$AUC_{0\text{-last}}$ Healthy	$AUC_{0\text{-last}}$ Mean Ratio	C_{max} Patients	C_{max} Healthy	C_{max} Mean Ratio
HD-CKD	Fexofenadine	P-gp, OATP1B3, OATP2B1	2.37 ng*h/mL	1.01 ng*h/mL	**2.3**	531 ng/mL	247 ng/mL	**2.2**
CKD Non-dialysis	Pitavastatin	**OATP1B1**, OATP1B3, BCRP, MRP2, UGT1A3, UGT2B7	164 ng*h/mL	126 ng*h/mL	**1.3**	74.3 ng/mL	63.1 ng/mL	**1.2**

Morgan RE, et al. *J Cardiovasc Pharmacol.* 2010;60:42-48; Thomson BK, et al. *Am J Kidney Dis.* 2015;65:574-582.

Microdose Study in Patients With Renal Impairment (RI)

- We conducted a study in patients with RI to examine the impact of RI on hepatic drug transporters
- We employed a microdose cocktail + endogenous biomarkers to
  - Assess the impact of RI on select drug transporter-mediated DDIs (focus on OATP1B as well as BCRP, P-gp)
  - Evaluate whether OATP1B endogenous biomarkers may serve as surrogates for DDI assessment in this population

Goal

Enhance our capability to ***predict*** drug PK and DDI risk for nonrenal elimination routes in patients with RI

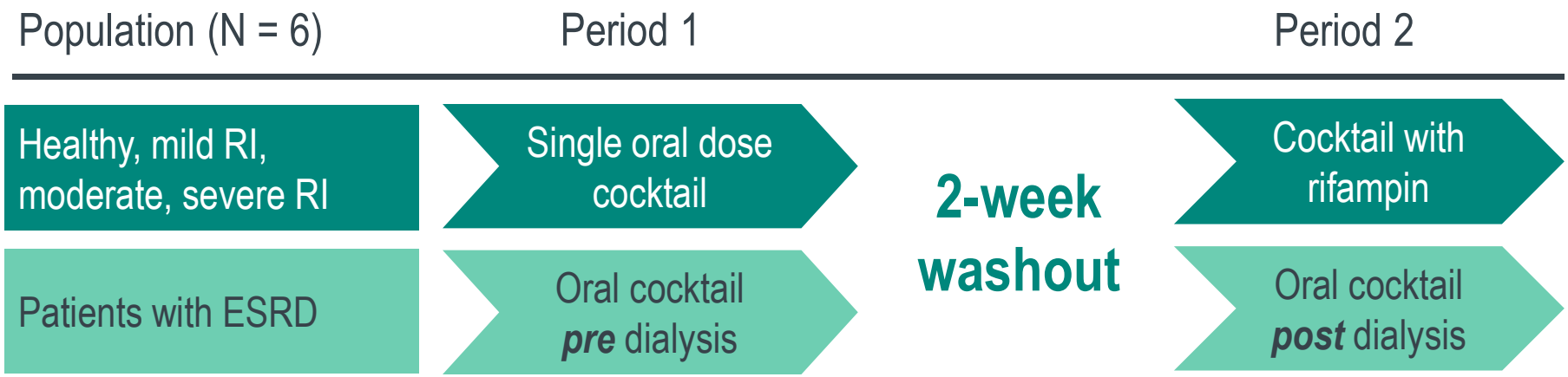
Selection of Probe Drugs

Probes in Microdose Cocktail*	Enzyme/Transport Pathway
10 µg pitavastatin	**OATP1B (selective and sensitive)**
50 µg rosuvastatin	**OATP1B1/OATP1B3/BCRP (liver and intestine)**
375 µg dabigatran etexilate	P-gp (prodrug only, intestine selective)
100 µg atorvastatin	CYP3A/OATP1B/BCRP/P-gp (liver and intestine)
10 µg midazolam	CYP3A4 (liver and intestine)

Perpetrator: 600-mg single-dose rifampin
(OATP1B/BCRP/P-gp inhibitor)

*Validated using rifampin, itraconazole, and clarithromycin as inhibitors (Prueksaritanont et al., CPT, 2016)

Study Population and Design



Measurements

- Plasma and urine PK for cocktail, with protein binding
- Endogenous biomarkers of OATP1B uptake (bilirubin, plasma coproporphyrin I and III, and sulfated bile acids)
- Uremic toxins (potential in vitro OATP1B inhibitors) were also measured

RI Increases Plasma Exposure of Pitavastatin, a Selective OATP1B Probe

Pitavastatin PK

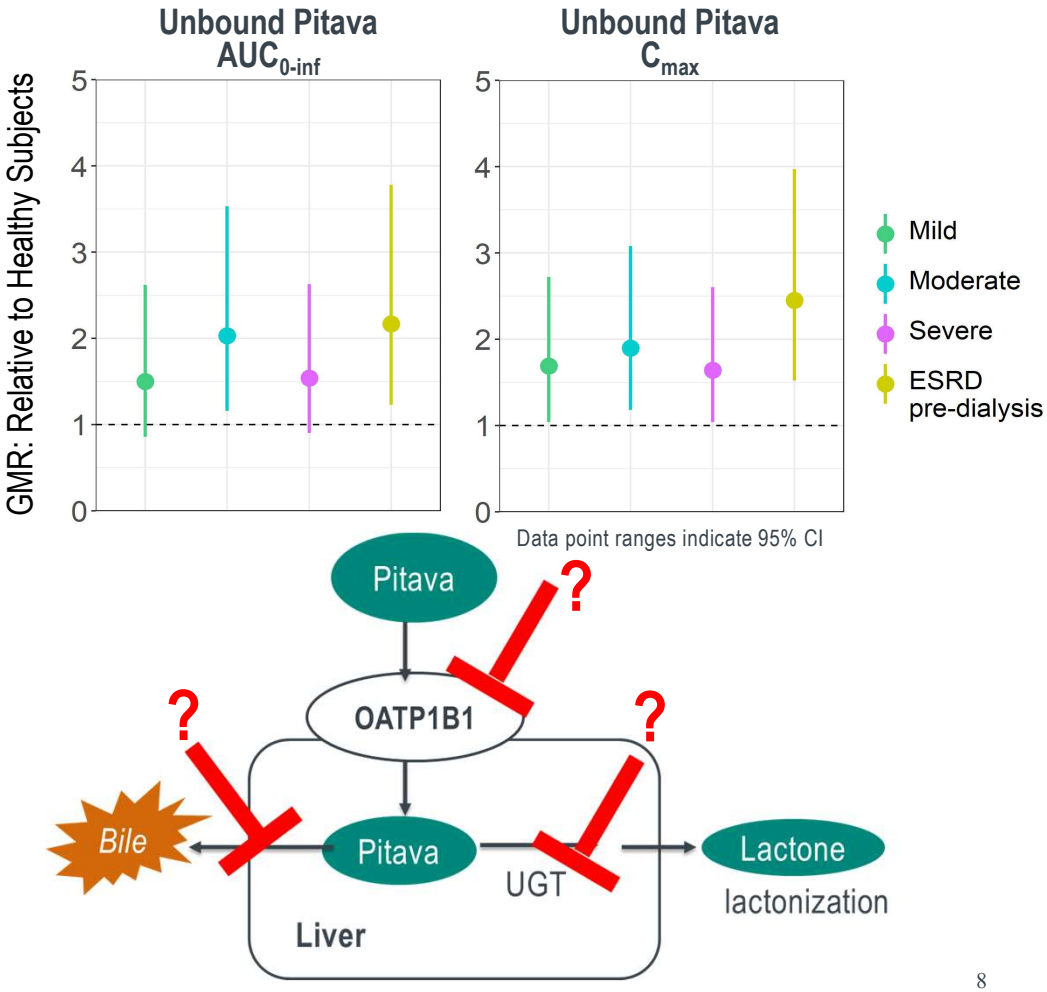
- High oral absorption (FaFg ~1)
- No known role of intestinal efflux
- Cleared by hepatic uptake, glucuronidation, and biliary excretion

RI increased pitavastatin PK without a clear trend with severity

- Consistent with recommended lower doses in mild to moderate groups in drug label

The causes for increased pitavastatin PK with RI are unknown, but could include

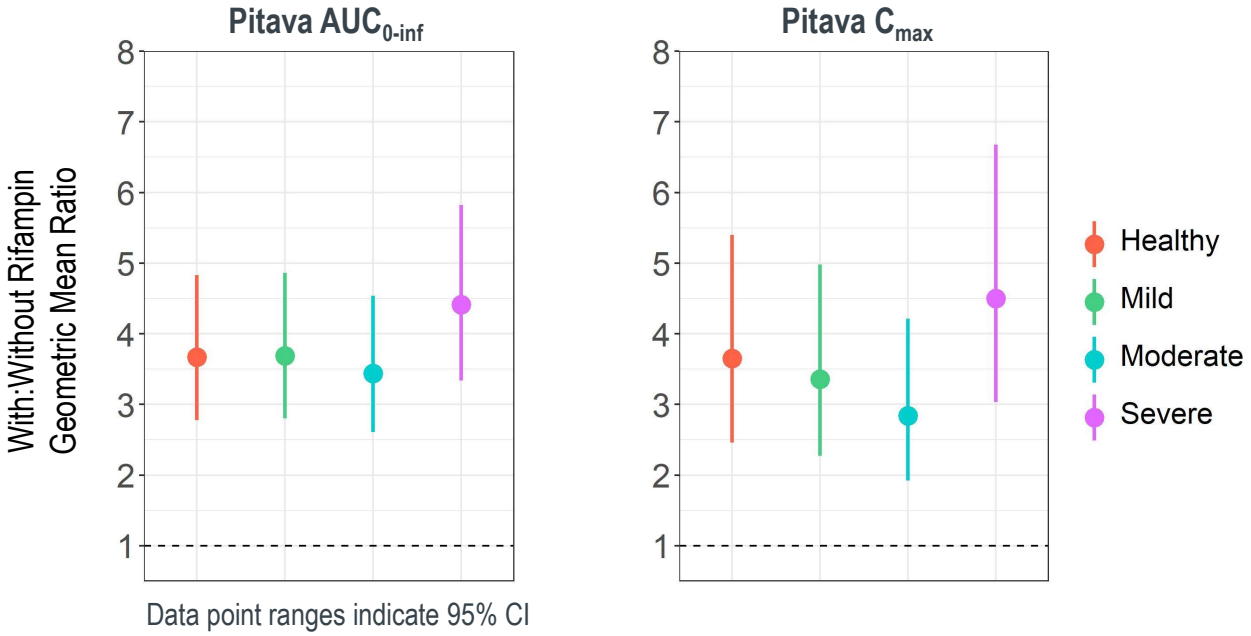
- ↓ hepatic OATP1B uptake
- ↓ UGT activity and/or biliary excretion



RI Does Not Alter Rifampin DDI With Pitavastatin

Rifampin caused ~4X increase in pitavastatin AUC and C_{max} across renal RI groups

- No apparent impact of RI on the extent of rifampin DDI
  - DDI results not consistent with a reduction in OATP activity with RI
- Results confirm pitavastatin as a sensitive OATP1B substrate



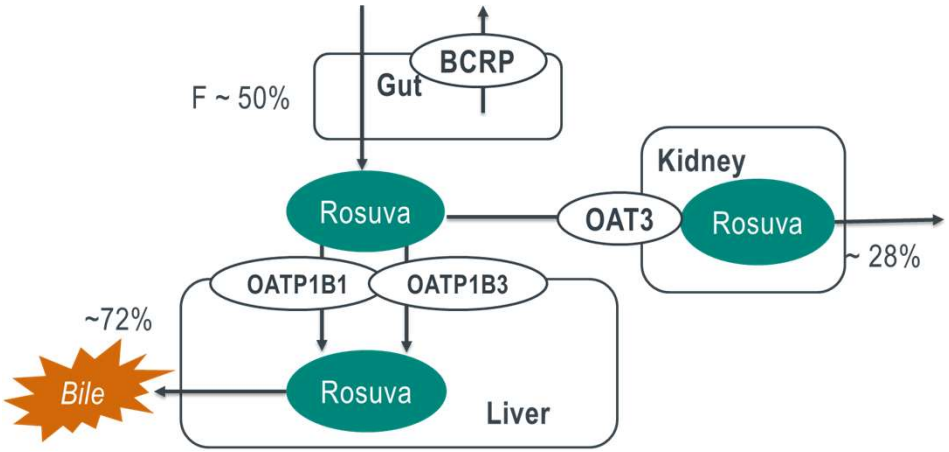
RI Did Not Significantly Alter Rosuvastatin Pharmacokinetics

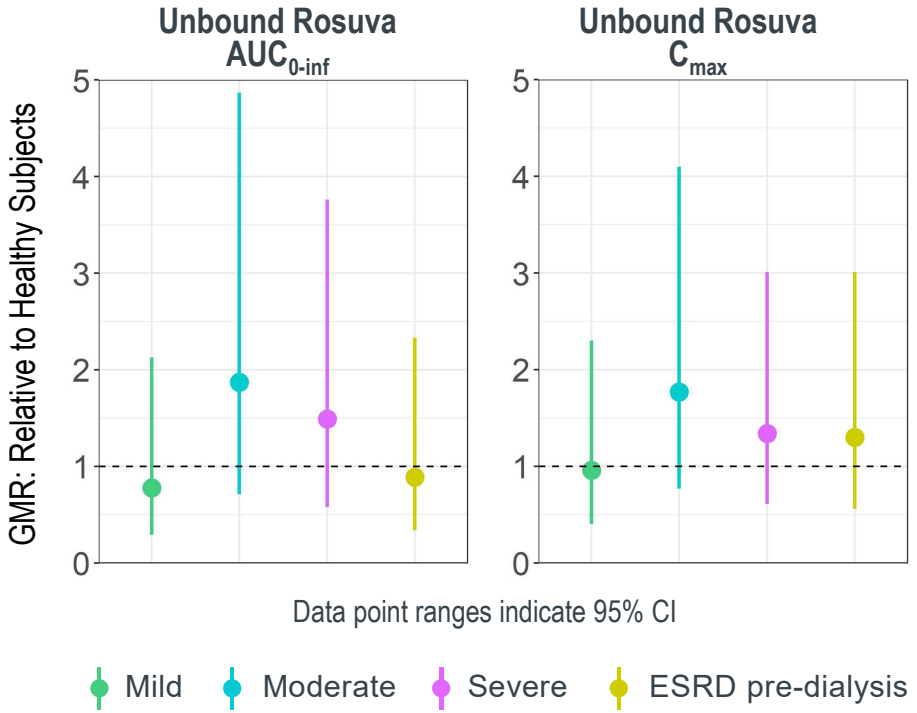
Rosuvastatin PK

- Substrate of OATP1B1/1B3 and BCRP
- Excreted in bile and urine (OAT3)

Results: Pharmacokinetics were highly variable without a clear trend with RI

- ↓ renal clearance up to 89% in severe RI





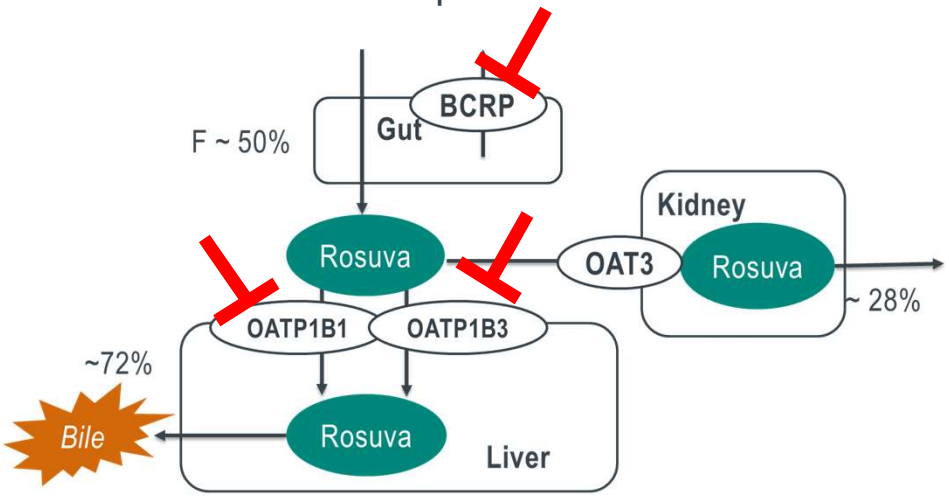
RI Did Not Alter Rifampin DDI With Rosuvastatin

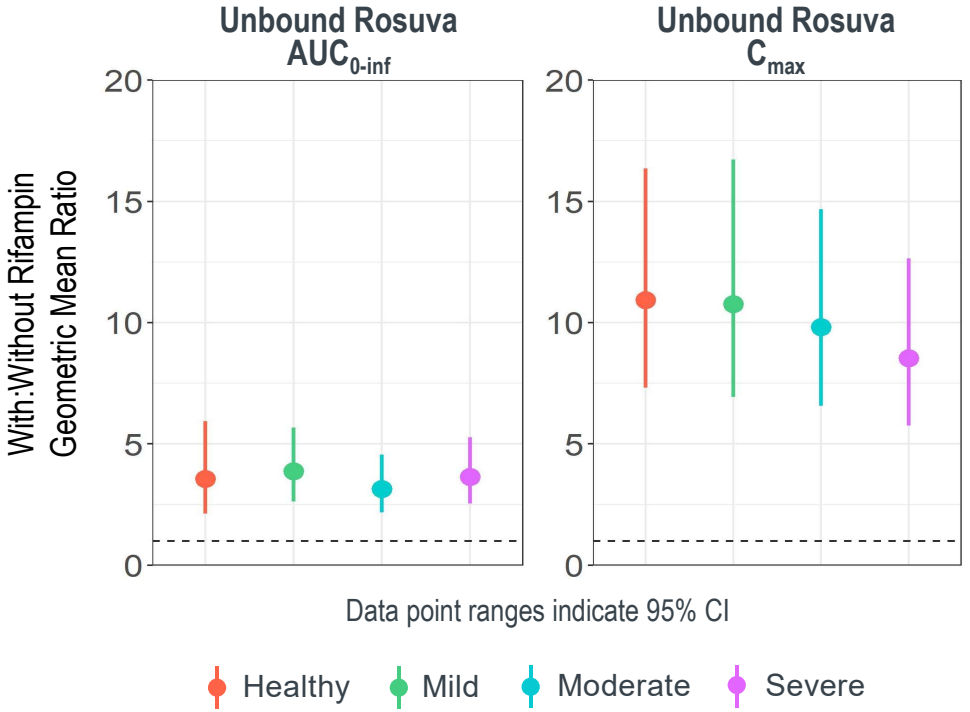
Rifampin caused ~3.5X ↑ AUC and ~10X ↑ C_{max}

- No trend with RI for AUC
- Possible slight trend for C_{max}

Unlike pitavastatin – C_{max} DDI > AUC

- Potential role of inhibiting BCRP on rate but not extent of absorption





Endogenous Biomarkers

- Evaluated endogenous biomarkers of OATP1B uptake
- Data can guide selection of biomarkers for deployment in drug development

Published Results: Impact of Rifampin on Endogenous Biomarkers in Healthy Subjects

Biomarkers	Literature Data	References
Coproporphyrin I and III (CPI/CPIII)	↑ 5.4-6.5 AUC	Shen, et al. 2016; Lai, et al. 2016[1,2]
Conjugated/unconjugated bilirubin	↑ 2-fold AUC	Chu, et al. 2015; Prueksaritanont, et al. 2014[3,4]
Sulfated bile salts (GDCA-S, GCDCA-S, DCA-S, TCDC-S, TCDA-S)	↑ 10-fold AUC	Takehara, et al. *Pharm. Res.* 2018[5]

1. Shen H, et al. *J Pharmacol Exp Ther.* 2016 May;357(2):382-93. 2. Lai Y, et al. *J Pharmacol Exp Ther.* 2016 Sep;358(3):397-404.
3. Chu X, et al. *Drug Metab Dispos.* 2015. 4. Prueksaritanont T, et al. *Br J Clin Pharmacol.* 2014 Sep;78(3):587-98.
5. Takehara I, et al. *Pharm Res.* 2018 May 10;35(7):138.

Coproporphyrins and Bilirubin Markedly Increased by Rifampin

CPI and CPIII: formed in liver, eliminated via hepatobiliary and renal excretion, with minimal metabolism

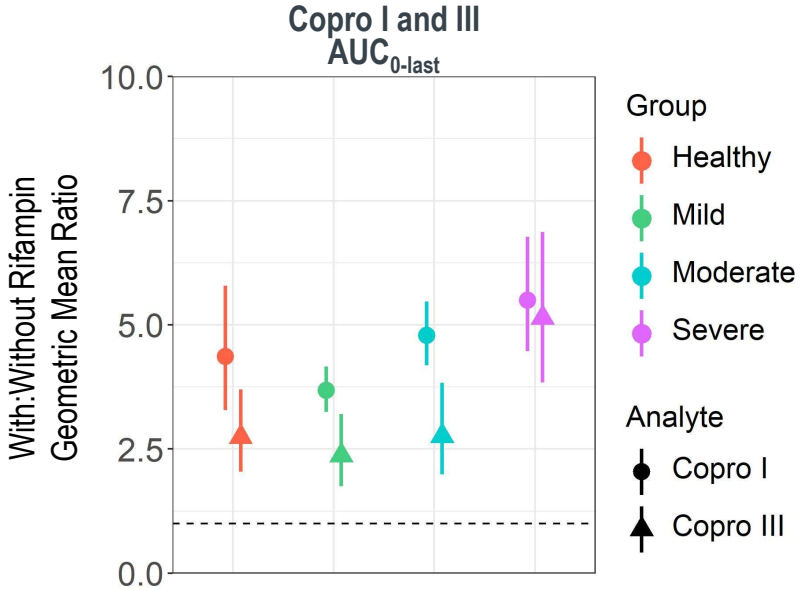
Bilirubin: complex hepatic disposition involving multiple transporters and enzymes

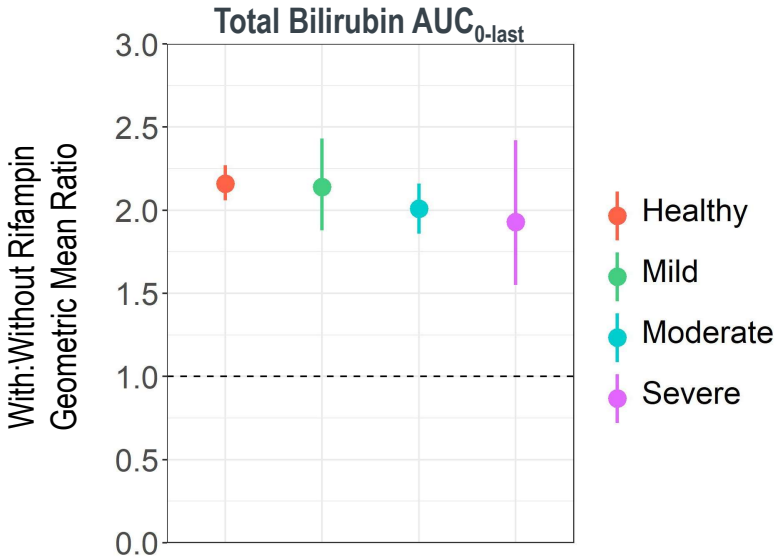
- All are substrates for OATP1B1/3

Rifampin ↑ AUC: ~2X for total bilirubin, 4X-6X for CPI, and 3X-5X for CPIII

Possible trend with severity noted for CPI/CPIII

- Coproporphyrin I – more sensitive OATP1B biomarker in all groups





Data point ranges indicate 90% CI of with:without rifampin GMR.

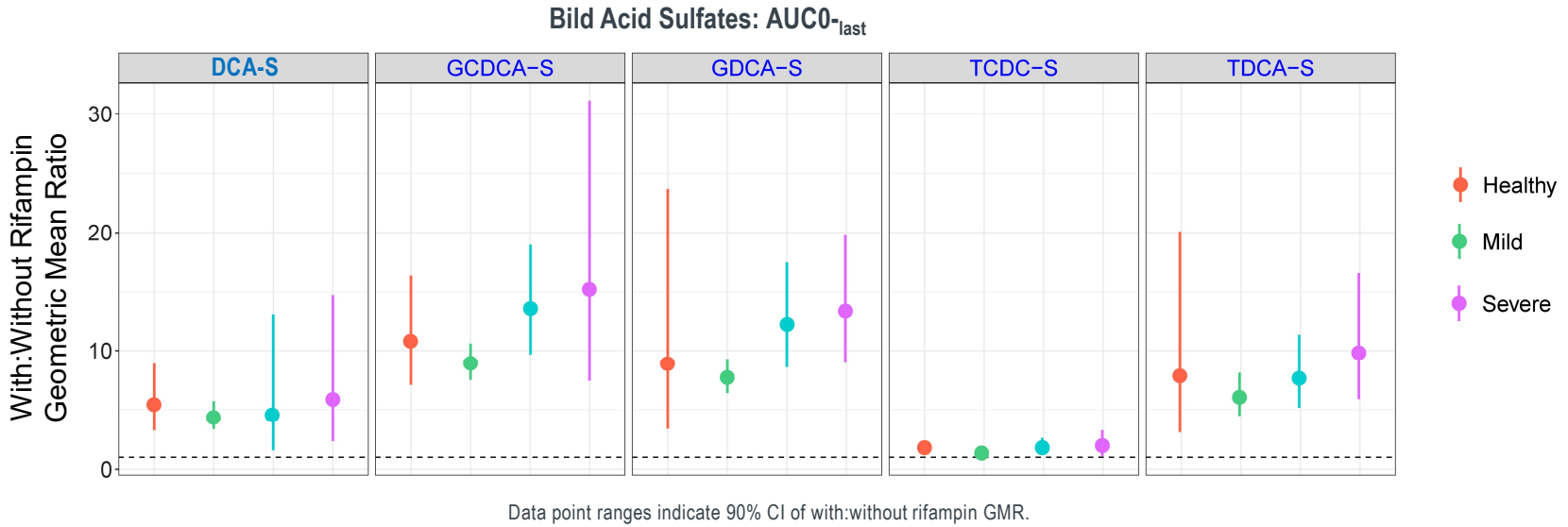
Sulfated Bile Acids Increased in Presence of Rifampin

Sulfated bile acids: formed in the liver from cholesterol, excreted into the bile, and mostly reabsorbed in the intestine after deconjugation

- Multiple transporters are involved (including OATP1B1/3)

Rifampin increased all sulfated bile acid AUCs

- GCDCA-S and GDCA-S appear more sensitive to rifampin
- Interaction appears to trend up with severity of RI for several analytes



Data point ranges indicate 90% CI of with:without rifampin GMR.

Conclusions

Impact of RI Severity on PK and Rifampin DDI

Probe	Pathway	RI vs HV PK	Rifampin DDI Trend With Increasing RI	Potential RI Impact on Transporters
Pitavastatin	OATP1B1	↑	↔	Unclear (DDI; not OATP1B?)
Rosuvastatin	OATP1B/BCRP	↔	↓ (C_{max})	↓ intestinal BCRP?
CPI/III, bile acid sulfate conjugates	OATP1B and other pathways	NA	↑	Other (not OATP1B, renal excretion?)

Mechanistic Insights

- Potential impact of RI on intestinal BCRP – weak effect of rosuvastatin
  - Impact of RI on transporters in the gut, not liver
- Rifampin DDI data not supportive of downregulation of OATP1B with RI

Acknowledgments

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