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Physiologically-Based Pharmacokinetics (PBPK) Modeling to Evaluate the Effect of Chronic Kidney Disease on the Disposition of Hepatically Eliminated Drugs

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Why assess CKD effect on nonrenally cleared drugs?

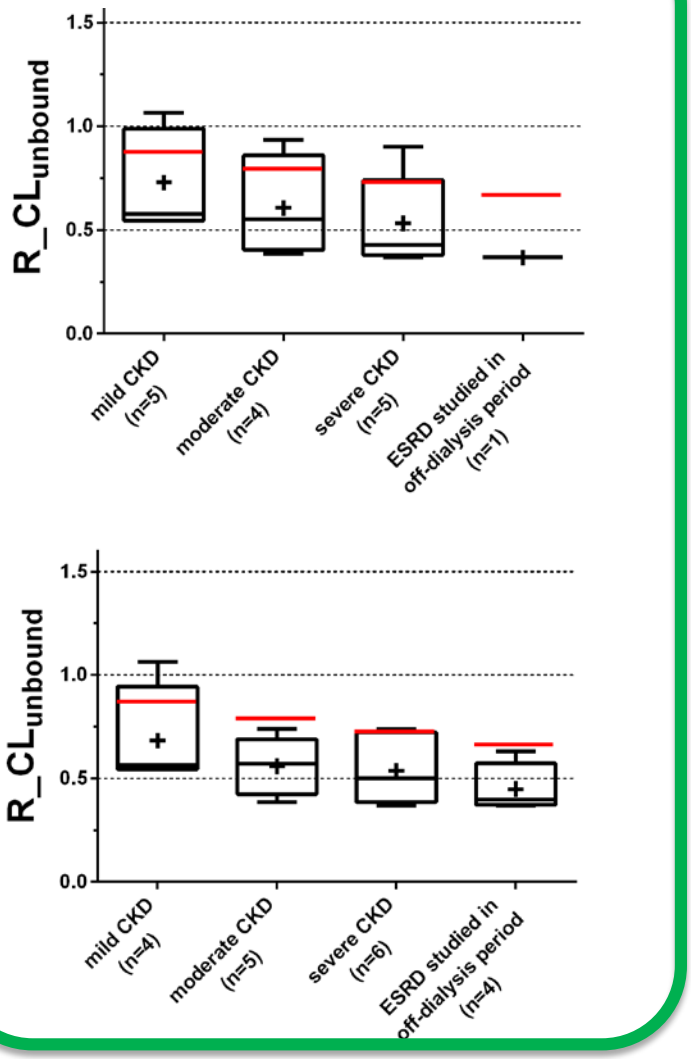
- Continued growth of Chronic Kidney Disease (CKD) population
- CKD can affect the pharmacokinetics of renally eliminated drugs
- CKD can also affect the pharmacokinetics of nonrenally eliminated drugs
- Critical to assess CKD effect on nonrenal pathways, but complex and challenging due to inconsistent PK alterations observed.

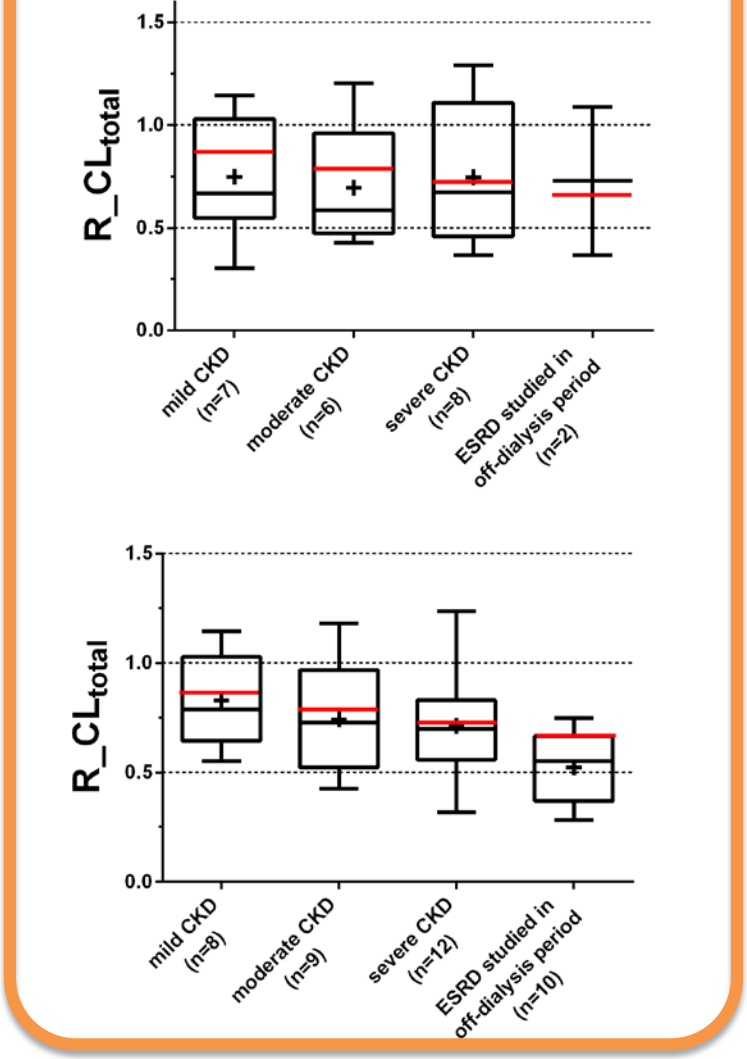
Effect of CKD on CYP2C8 and OATP

- ✓ CL ratio generally decreases as the CKD severity increases

CYP2C8

OATP1B





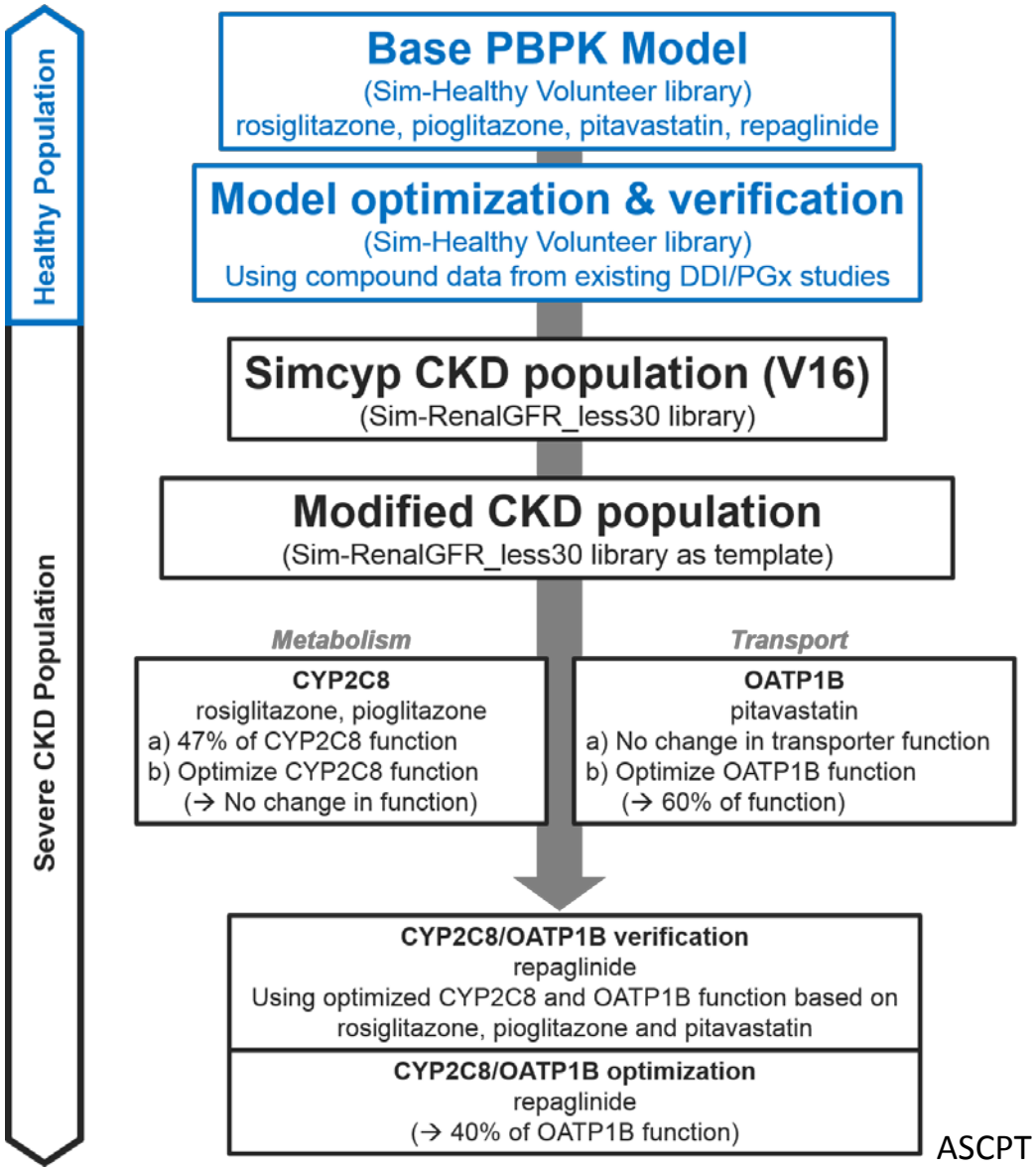
Tan M-L *et al.*, *Clin Pharmacol Ther.* 2017 Oct 9 [Epub ahead of print]

Effect of CKD on nonrenally eliminated pathways

- CKD **differentially** affects the PK of nonenally cleared drugs
  - Limited effect on CYP1A2, CYP2C9, CYP2C19, CYP3A4/5 mediated CL
  - **CYP2D6** and **OATP** mediated drug CL generally ↓ as CKD severity ↑
  - CYP2C8 mediated CL: a similar decreasing trend observed, but inconclusive due to the overlap with OATP substrates
- Is a mechanistic understanding possible to quantify the individual contribution of metabolic enzymes (e.g., CYP2C8) and hepatic transporters (e.g., OATP)?
  - CYP2C8 substrates: rosiglitazone, pioglitazone
  - OATP substrate: pitavastatin
  - CYP2C8/OATP dual substrate: repaglinide

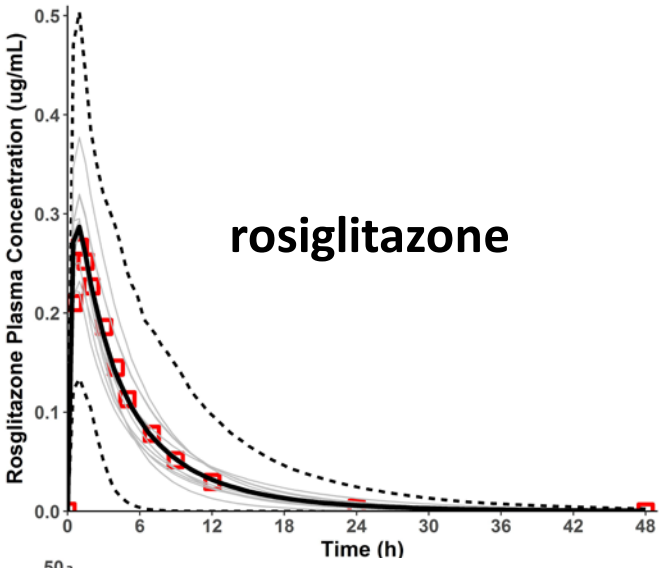
Yoshida K *et al.*, *Clin Pharmacol Ther.* 100, 75 (2016)
Tan M-L *et al.*, *Clin Pharmacol Ther.* 2017 Oct 9 [Epub ahead of print]

Workflow to predict drug PK in RI using PBPK

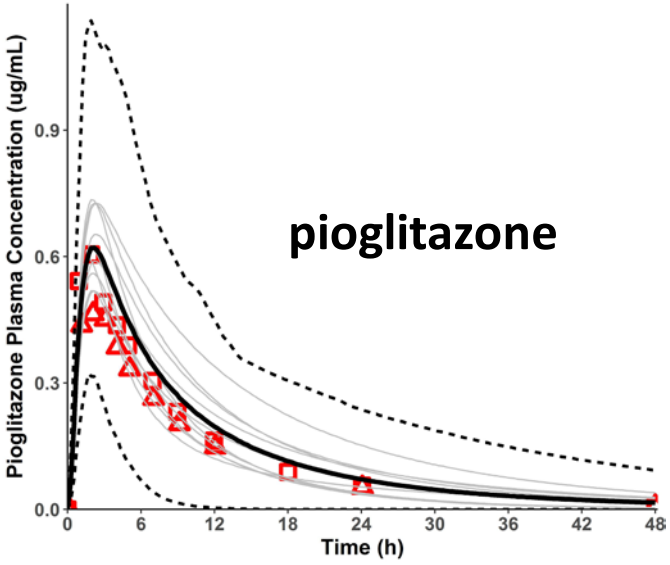


ASCPT poster number: **PT-007**
Tan M-L *et al*, to be submitted

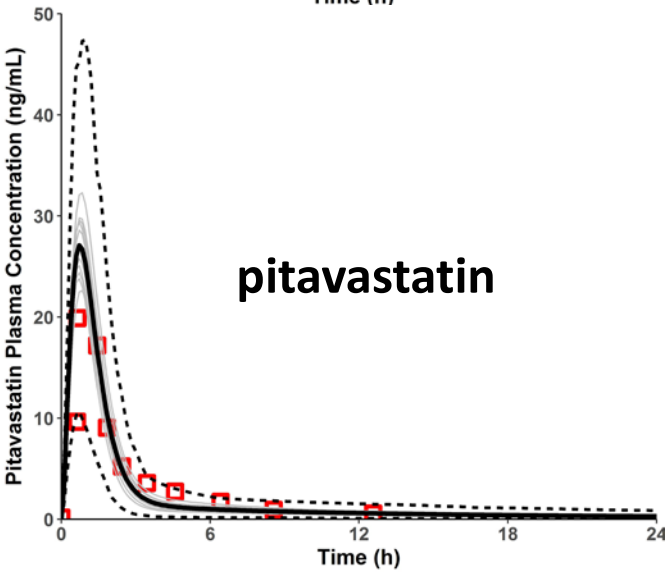
PBPK Model Optimization and Verification in HV



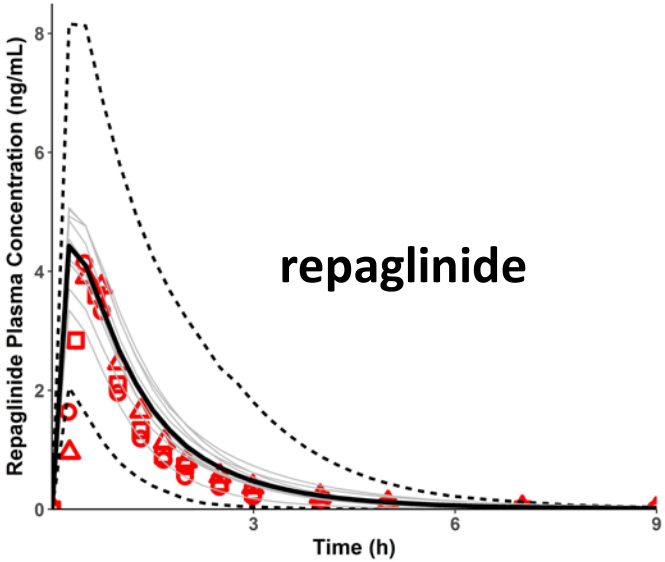
rosiglitazone



pioglitazone



pitavastatin



repaglinide

DDI and PGx: The predicted AUCR values were within two-fold of the observed data

CKD Effect on CYP2C8 substrate drugs

Substrate Drug	CKD populations	fu (%) HV	fu (%) CKD	AUCR (total) Simulated	AUCR (total) Observed	R value	AUCR (unbound) Simulated	AUCR (unbound) Observed	R value
Rosiglitazone	Simcyp (CYP2C8 47%)	0.16	0.22	1.44	0.81	1.78	2.47	1.11	2.23
	Modified (CYP2C8 100%)	0.16	0.22	0.93	0.81	1.14	1.58	1.11	1.42
Pioglitazone	Simcyp (CYP2C8 47%)	3	*3.5*	1.58	0.78	2.03	2.40	*0.92*	*2.6**
	Modified (CYP2C8 100%)	3	*3.5*	0.90	0.78	1.15	1.36	*0.92*	*1.48*

- Approximate two-fold overprediction when using default Simcyp
- Comparable to the observed values when modified population was used assuming no change in the CYP2C8 function from the HV

→ **Minimal changes in CYP2C8 activity in severe CKD population**

Tan M-L *et al.,* to be submitted

CKD Effect on OATP substrate drug

Substrate Drug	CKD populations	fu (%) HV	fu (%) CKD	AUCR (total) Simulated	AUCR (total) Observed	R value	AUCR (unbound) Simulated	AUCR (unbound) Observed	R value
Pitavastatin	Simcyp (CYP2C8 47%,OATP100%)	0.6	0.6	0.85	1.36	0.63	1.05	1.36	0.77
	Simcyp (CYP2C8 47%,OATP 60%)	0.6	0.6	1.28	1.36	0.94	1.59	1.36	1.17
	Modified (CYP2C8 100%,OATP100%)	0.6	0.6	0.84	1.36	0.62	1.04	1.36	0.77
	Modified (CYP2C8 100%,OATP60%)	0.6	0.6	1.28	1.36	0.94	1.59	1.36	1.17

- Under predicted when using default Simcyp severe CKD population
- OATP1B activity needs to be reduced to up to 60% in order to match the observed AUCR

→ **Decreased OATP1B activity is likely in severe CKD population**

Tan M-L *et al.,* to be submitted

CKD Effect on CYP2C8/OATP Substrate Drug

Substrate Drug	CKD populations	fu (%) HV	fu (%) CKD	AUCR (total) Simulated	AUCR (total) Observed	R value	AUCR (unbound) Simulated	AUCR (unbound) Observed	R value
Repaglinide	Simcyp (CYP2C8 47%,OATP100%)	3.6	3.6	1.37	2.72	0.51	1.72	2.72	0.63
	Simcyp (CYP2C8 47%,OATP 50%)	3.6	3.6	2.55	2.72	0.94	3.18	2.72	1.17
	Modified (CYP2C8 100%,OATP100%)	3.6	3.6	1.08	2.72	0.40	1.35	2.72	0.50
	Modified (CYP2C8 100%,OATP60%)	3.6	3.6	1.72	2.72	0.63	2.14	2.72	0.79
	Modified (CYP2C8 100%,OATP45%)	3.6	3.6	2.20	2.72	0.81	2.75	2.72	1.01
	Modified (CYP2C8 100%,OATP40%)	3.6	3.6	2.43	2.72	0.89	3.03	2.72	1.11

- Under predicted (~50% of the observed values) when using default Simcyp severe CKD population
- A little under predicted when used OATP reduced to 60% from pitavastatin study
- OATP1B activity needs to be reduced to ~ 40% in order to match the observed AUCR

→ **Decreased OATP1B activity is likely in severe CKD population**

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Conclusions

- The base models reasonably captured the corresponding PK profiles for rosiglitazone, pioglitazone, pitavastatin and repaglinide in healthy subjects using Simcyp v16.
- The PBPK models were further verified by simulating the clinical DDI and PGx studies.
- No reduction in CYP enzyme function was required to match the AUCR for CYP2C8 substrates.
- Decreases in OATP1B activity of up to 60% were needed to match the change in AUC observed in severe CKD subjects.
- CYP enzyme and transporter interplay can be modeled through PBPK modeling.

Acknowledgment

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- US Food and Drug Administration's Medical Countermeasures initiative.

Thank you!

Backup Slides

PBPK Models

Parameters	Rosiglitazone[a]	Pioglitazone[b]	Pitavastatin[c]	Repaglinide[d]
Physicochemical properties				
Molecular weight (g/mol)	357.4	356.4	421	452.6
Compound type	Ampholyte	Monoprotic acid	Monoprotic acid	Ampholyte
Log P	2.6	3.5	2.91	4.87
pKa	6.25 and 6.32	5.53	5.31	4.19 and 5.78
f_u	0.002	0.015	0.005	0.015
Blood/plasma ratio	0.57	1	0.55	0.62
Absorption				
Absorption type	First order	ADAM	ADAM	First order
Fraction absorbed	1 (k_a=3.6 /h)	0.98	0.99	0.997 (k_a=2.8 /h)
Peff, man (10^{-4} cm/s)	1.291	3.754	4.688	6.490
Absorption scalar	1	1	1	1.873
Distribution				
Distribution model	Minimal PBPK	Minimal PBPK	Full PBPK (method 2[e]) Kp scalar 1	Full PBPK (method 2[e]) Kp scalar 2.42**
V_{SS} (l/kg)	0.12	0.253	1.88	0.256
Elimination				
$CL_{int,CYP2C8}$ (µl/min/mg protein)	191 (HLM)	27.5 (HLM)	12.98 (rCYP) (µl/min/pmol)	93 (HLM)
$CL_{int,CYP2C9}$ (µl /min/mg protein)	102 (HLM)	1.5 (HLM)	7.93 (rCYP) (µl/min/pmol)	
$CL_{int,CYP2C19}$ (µl /min/mg protein)		6.1 (HLM)		
$CL_{int,CYP3A4}$ (µl /min/mg protein)				38 (HLM)
$CL_{int,others}$ (ml/min/mg protein)			1.453	
Renal clearance (l/h)	0.32	0	0.129	0
Hepatobiliary transport				
Liver unbound fraction (Intra-/extracellular)			0.460/0.0096	0.143/0.028
Passive diffusion (ml/min/10^6cells)			0.011	0.024
$CL_{int,active}$ (ml/min/10^6cells)			0.0584 (OATB1B1), 0.0051 (OATP1B3)[f]	0.037 (OATP1B1)
Scaling factor (OATP active uptake)			15*	16.9

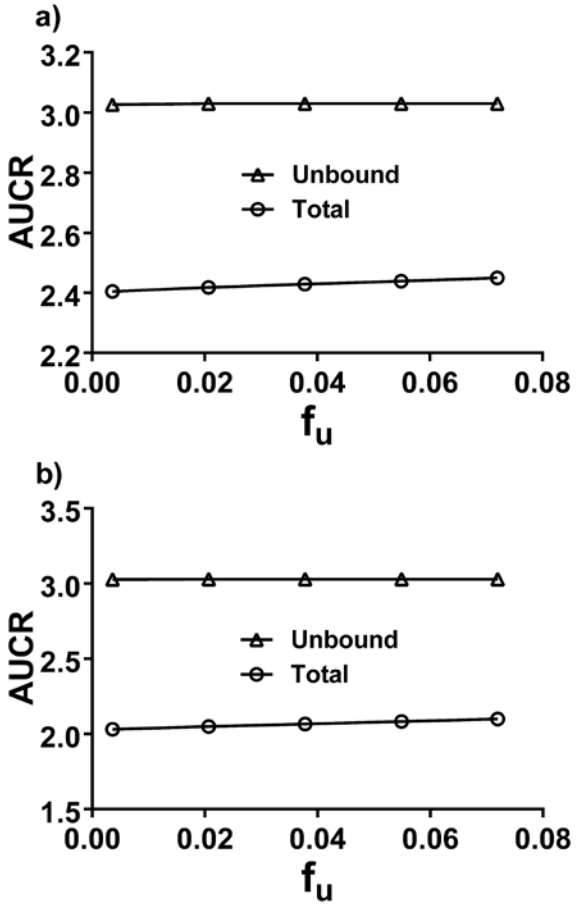
DDI and PGx Studies

Drugs	*SLCO1B1* polymorphism or drug inhibitor	Simulated AUCR	Observed AUCR	R value
Rosiglitazone	Gemfibrozil	2.41	2.36	1.02
Pioglitazone	Gemfibrozil	3.84	3.2	1.20
Pitavastatin	*SLCO1B1* polymorphism (c. 521 CC vs c. 521 TT)	1.90	3.08	0.62
	Gemfibrozil	1.58	1.45	1.09
	Cyclosporine	3.29	4.55	0.72
Repaglinide	*SLCO1B1* polymorphism (c. 521 CC vs c. 521 TT)	1.88	1.83	0.97
	Gemfibrozil	3.22	5.0	0.64
	Cyclosporine	2.79	2.4	1.16

All the predicted AUCR values were within two-fold of the observed data

Tan M-L et al, to be submitted

Sensitivity analysis on unbound fraction fu for repaglinide



a) The CKD populations with same f_u as the HV as observed in the corresponding clinical studies

b) The CKD populations with f_u estimated based on the f_u of HV using the information on the changed albumin levels

AUCR not sensitive to changes in plasma f_u within values between 0.37% and 7.2%

Limitations

1) Modeling approach focused primarily on the activity of major proteins and ignored other potential minor pathways that may gain more relevance in CKD patients, such as P-gp, BCRP for Pitavastatin and different UGTs.
2) Minor CYP enzyme pathways CYP2C9, CYP2C19, CYP3A4 used Simcyp default. Verifications needed for CKD.
3) Some inconsistencies were observed in terms of the level of decrease in OATP1B function required for pitavastatin and repaglinide.

"Several preclinical studies demonstrated that uremia leads to decreased function and expression of metabolizing enzymes and transporters in intestine and liver. However, direct measurement of protein levels and activities in human CKD patients may be needed to confirm the actual mechanism."

References

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2 .Leblond, F.A., Petrucci, M., Dubé, P., Bernier, G., Bonnardeaux, A. & Pichette, V. Downregulation of intestinal cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* **13**, 1579-85 (2002).
3. Naud, J. *et al.* Down-regulation of intestinal drug transporters in chronic renal failure in rats. *J Pharmacol Exp Ther* **320**, 978-85 (2007).
4. Naud, J., Michaud, J., Leblond, F.A., Lefrancois, S., Bonnardeaux, A. & Pichette, V. Effects of chronic renal failure on liver drug transporters. *Drug Metab Dispos* **36**, 124-8 (2008).

Tan M-L et al, *Clin Pharmacol Ther.* 2017 Oct 9 [Epub ahead of print]

Effect of genetic polymorphism on AUC

Simcyp: relative abundance for *SLCO1B1* genotype

ET	IT	PT	UT
1	0.68	0.37	1.47

Assumed: population with SLCO1B1 c. 521 TT <- subjects with 100% of ET
population with SLCO1B1 c.521 CC <- subjects with 100% of PT

Drugs	Simulated AUCR	Observed AUCR	R (AUCRs/AUCRo)
repaglinide	1.88	1.83[a], 2.90[b]	0.97, 0.65
pitavastatin	1.90[c]	3.08[c]	0.62[c]

[a]0.25 mg single oral dose. c. 521 TT: 5 male and 7 female, 24±4 yrs, 171±8cm, 71±12kg; 521 CC: 3 male and 5 femal, 24±5 yrs, 172±7cm, 70±6kg

[b]0.25 mg single oral dose. c. 521 TT: n=36; c. 521 CC: 4

[c]The simulated ratio of c. 521 CC and c. 521 TT was compared to the observed ratio of "*15/*15 421C/C 421C/A" and "*1b/*1b 421C/C" since no genotyped "*15/*15 421C/C" was reported (Ieiri et al, *CPT* 82, 541 (2007)).

The R values (simulated AUCR to observed AUCR) are within two folds

Simcyp: no relative abundance information available for CYP2C8 genotype (no simulation is done so far)

f_m

Simulated f_m (%) using the PBPK models

Drugs	CYP2C8*	CYP2C9	CYP2C19	CYP3A4	Renal
rosiglitazone	52 (56)	29			19
pioglitazone	75 (79)		19	6	
repaglinide	64 (88)			36	
cerivastatin	54 (77)			46	

*$f_{m,CYP2C8}$ in the parenthesis is from the Table 3 of the accepted CKD paper, which was calculated from the maximum AUCR of the clinical DDI with gemfibrozil

Pitavastatin f_t: OATP1B1 (87.5%), OATP1B3(11.1%) and passive diffusion (1.4%)

fa, Fg, Fh, F

Simulated properties using the PBPK models

Drugs	f_a	Fg	Fh	F
rosiglitazone	0.87	0.87	0.96	0.73
pioglitazone	0.97	0.99	0.96	0.92
Pitavastatin	0.98	1.0		
repaglinide	0.99	0.93	0.89	0.82

Three methods to interpret the observed CL ratios

1. Theoretical lowest values in CL: assuming CKD has no effect on respective nonrenal pathways.

2. Using individually estimated contribution of the pathway of interest, $f_m = 1 - \frac{1}{AUCR}$

$$R\_CL_{obs} = R\_CL_{CYP} \times f_m + R\_CL_r \times (1 - f_m)$$

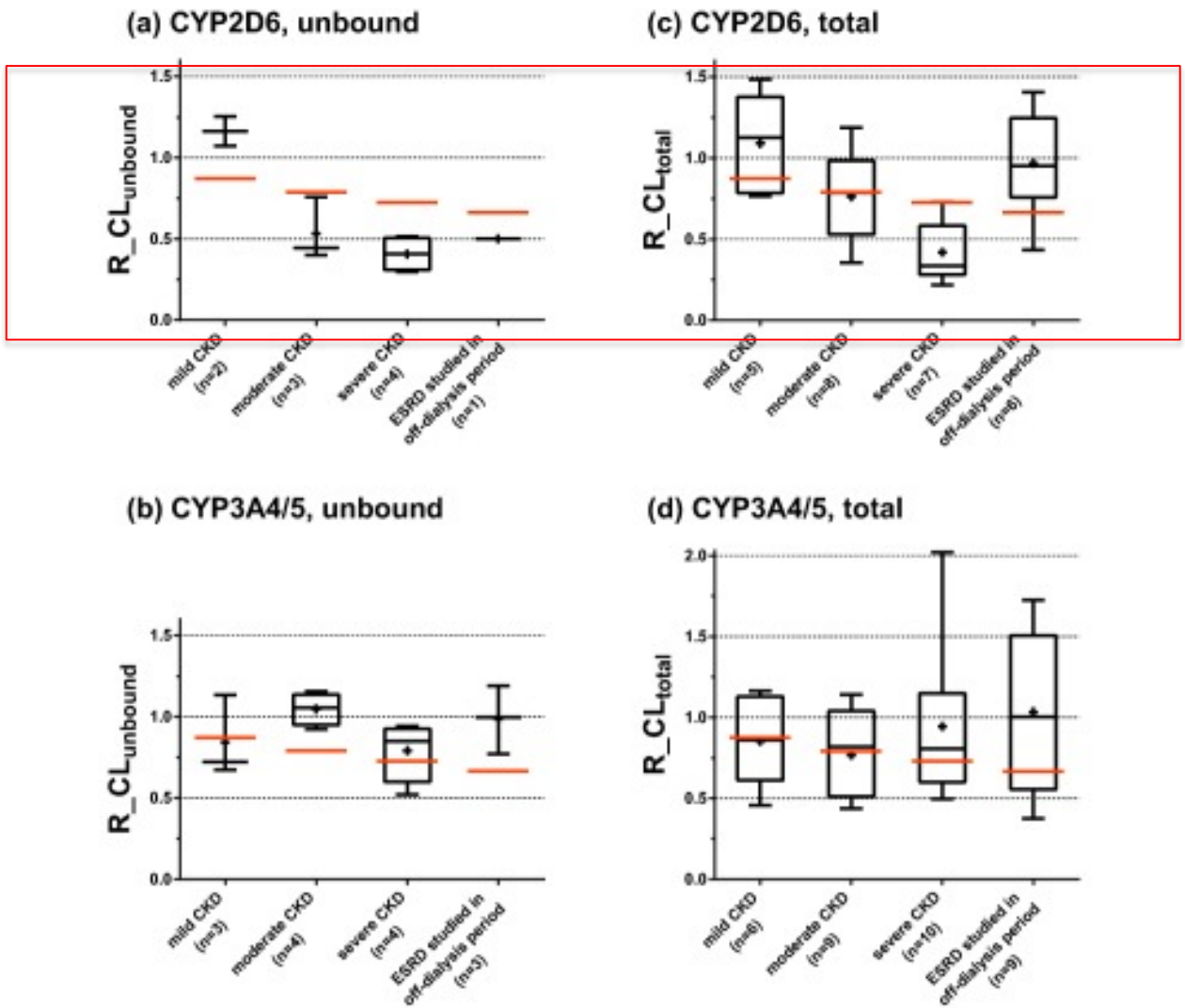
Therefore,

$$R\_CL_{CYP} = \frac{R\_CL_{obs} - R\_CL_r \times (1 - f_m)}{f_m}$$

3. Using $f_{e,urine}$

$$R\_CL_{CYP} = \frac{R\_CL_{obs} - R\_CL_r \times f_{e,urine}}{1 - f_{e,urine}}$$

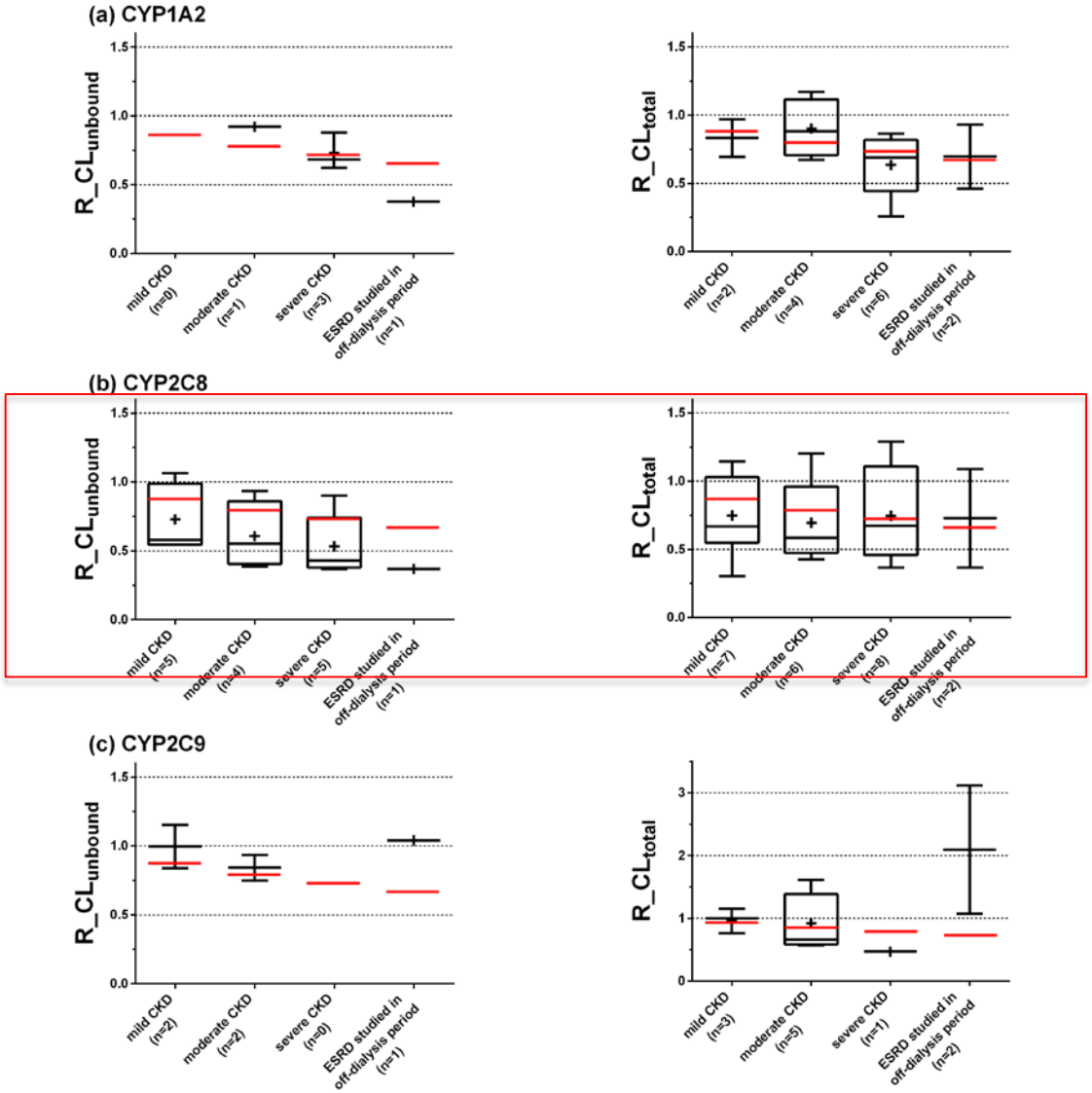
Effect of CKD on CYP2D6 and 3A4/5



CYP2D6: affected; while CYP3A4/5: variable and minimal

Yoshida K et al, *Clin Pharmacol Ther.* 100, 75 (2016)

Effect of CKD on CYP1A2, CYP2C8 and CYP2C9



CYP2C8: maybe affected? while CYP1A3 and CYP2C9: variable and minimal

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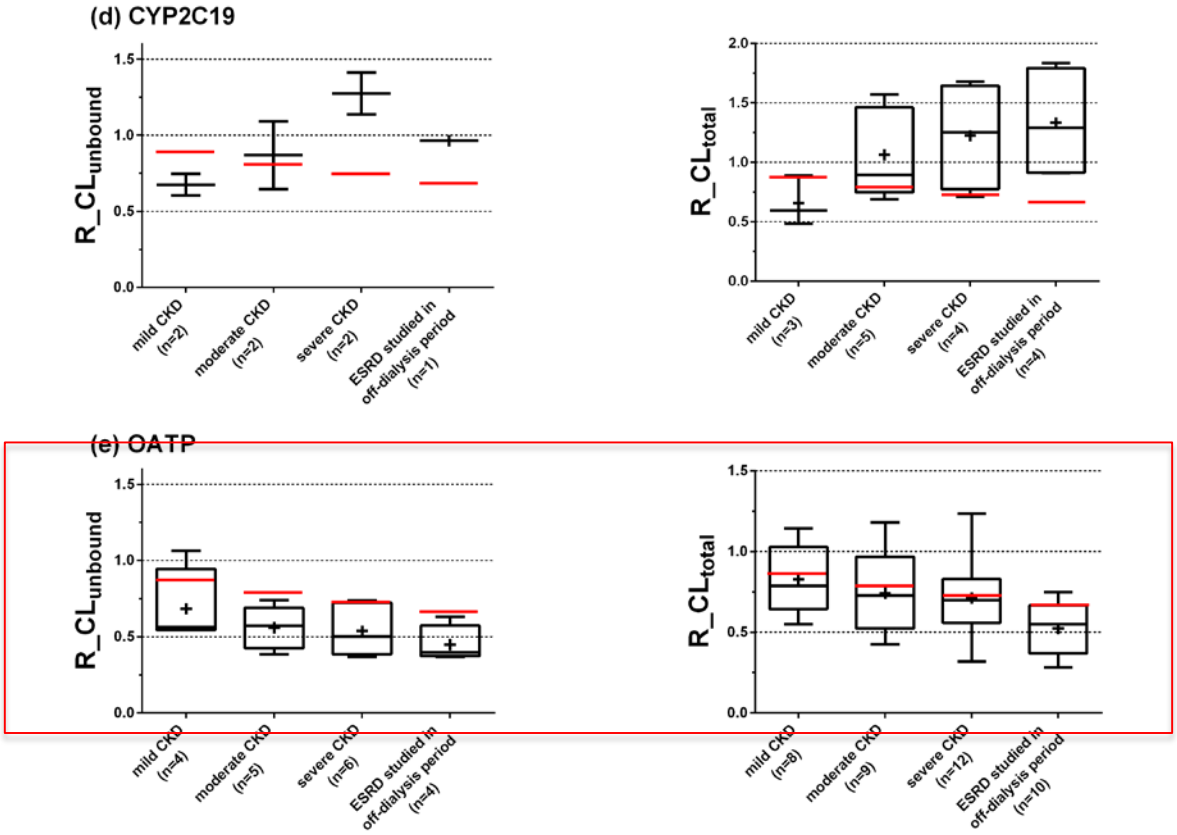
Effect of CKD on 2C19 and OATP1B



OATP: affected; while CYP2C19: variable and minimal

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PK parameters in CKD patients

OATP model substrate drugs

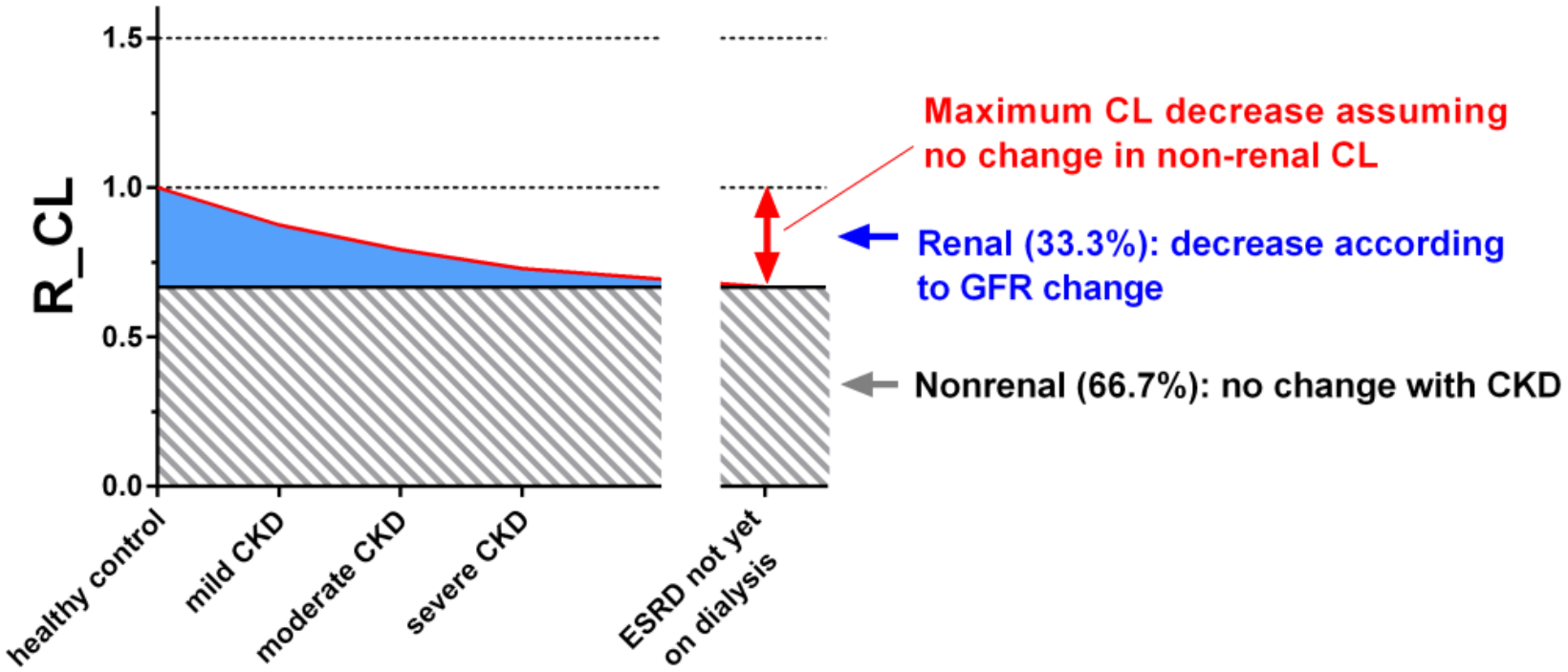
Drugs	$f_{e,urine}$ [a]	DDI with maximum OATP AUCR			PGx with maximum OATP AUCR			References [g]
		AUCR	f_t	Inhibitors	AUCR	f_t	PGx	
atorvastatin	< 0.02 [b]	12	0.92	rifampin	2.45	0.59	NF vs PF	PL, (92, 93)
bosentan	< 0.03 [b]	5.22 [c]	0.81	lopinavir & ritonavir [c]	-	-	-	PL, (94)
cerivastatin	< 0.02 [b]	4.75	0.79	cyclosporine	-	-	-	(39, 95)
erythromycin	0.12	-	-	-	2.60 [f]	0.62	NF vs PF	(62, 96)
fexofenadine	0.20 [b]	4.14 [d]	0.76	lopinavir and ritonavir [d]	-	-	-	(97, 98)
fluvastatin	0.21 [b]	3.55	0.72	cyclosporine	2.39	0.58	NF vs PF	(63, 99, 100)
imatinib	0.051 [b]	-	-	-	2.58 [f]	0.61	NF vs PF	PL, (101)
pitavastatin	0.059 [b]	6.66	0.85	rifampin	3.85	0.74	NF vs PF	(30, 65), NDA 022363, (102)
simeprevir	0.15 [b]	5.80	0.83	cyclosporine	-	-	-	PL, (103)
repaglinide	0.001 [b]	2.60 [e]	0.62	cyclosporine [e]	3.13	0.68	NF vs PF	(78, 79, 104, 105)
rosuvastatin	0.28	7.08	0.86	cyclosporine	2.19	0.54	NF vs PF	NDA 021366, (106, 107)
torsemide	0.282	-	-	-	2.51 [f]	0.60	NF vs PF	(66, 108)

NF, normal function; NDA, new drug application; PGx, pharmacogenetics; PF, poor function; PL, from Product Label (https://dailymed.nlm.nih.gov); PM, poor metabolizer. f_t = 1-1/AUCR for transporter

Theoretical Lowest CL ratio

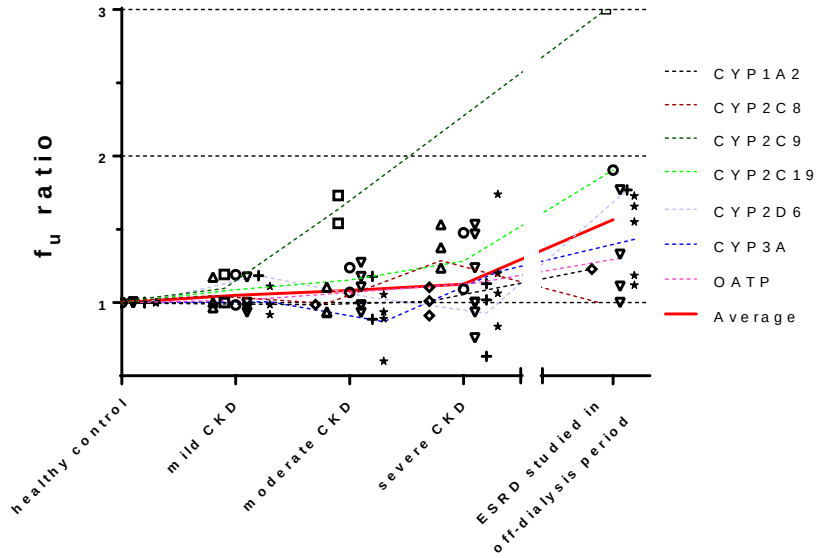
Theoretical lowest CL ratio:

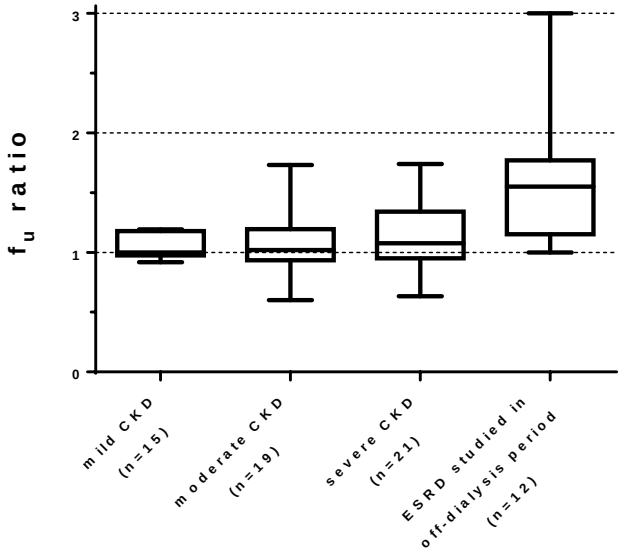
- Assumptions (if AUCR≥3)
- Equations (theoretical lowest CL ratio): **R_CL = 66.7% + 33.3%×[% of renal activity in each RI group]**



If observed R_CL of a test drug is lower than the "Theoretical lowest R_CL", the drug's nonrenal pathways may have been impaired in CKD subjects

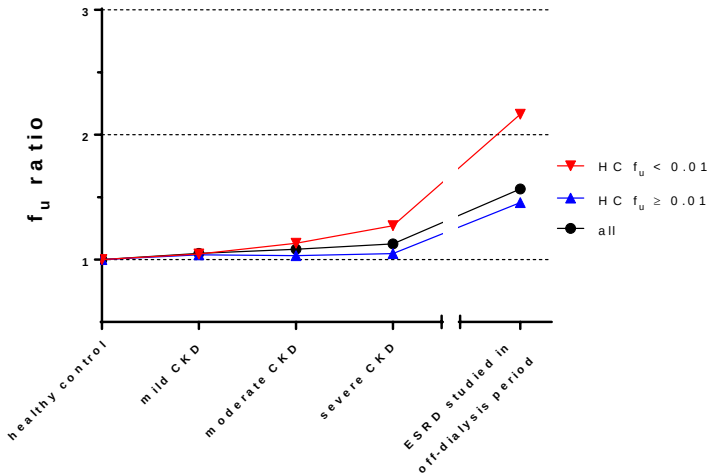
Effect of CKD on Plasma Unbound Fraction





Symbols (CYP1A2(◊), CYP2C8(Δ), CYP2C9(□), CYP2C19(○), CYP2D6(Δ), CYP3A4(+) and OATP(*)

The f_u ratio is decreased with the severity of CKD for the nonrenally eliminated drugs investigated



The increasing trend appeared to be more prominent for drugs with higher f_u.

Estimation of unbound fraction for OATP/ CYP2C8 model drugs missing fu

For acidic drugs, the decreased plasma protein binding is often observed to be related to the reduced albumin levels in plasma. Due to limited availability of data on the main proteins relevant for plasma binding of most drugs in the dataset, the missing f_u was estimated for severe CKD group using the information on the changed albumin levels relative to healthy control, assuming albumin is the dominant binding protein

$$fu = \frac{1}{1+[\frac{[P]}{[P]pop}\times\frac{(1-fu\,pop)}{fu\,pop}]}$$

where pop is the healthy population, $[P]_{pop}$ is the average concentration of albumin in the plasma of healthy population (44.9 g/l for male and 41.8 g/l for female) and [P] is the average concentration of albumin in the plasma of severe CKD (37.6 g/l for male and 35 g/l for female), respectively

Effect of CKD on Absorption

- ↑ gastric pH ..... Urea, drugs
  - Salivary urease converts urea to ammonia
  - Altered dissolution/ionization and F
  - Furosemide (*Clin Pharmacol Ther* 1978;23:644)
    - 37% ↓ F (0.689 healthy vs. 0.434 CKD; $p<0.05$)
- ↓ gastric emptying ..... Gastroparesis
  - May ↑ t_{MAX}, ↓ C_{MAX} with no change in AUC and F
  - Rate of absorption ↓, but extent unchanged
- ↓ 1st pass effects ..... ↑ F
  - β-blockers (*Int J Clin Pharmacol Res* 1983;3:459)
- Local interactions ..... chelation, ↓ F
  - Antacids, phos binders, enteral feeds + cipro
    - ↓ F cipro by 28%-51% (*Blood Purif* 2007;25:133)

Slide courtesy of Tom Nolin

Effect of CKD on Distribution

- ↓ protein binding, ↑ f_u ..... ↑ V_d
  - Hypoalbuminemia
    - Acidic drugs primarily affected (e.g., penicillins, cephalosporins, furosemide, salicylates, phenytoin)
  - Phenytoin (*Eur J Clin Pharmacol* 1974;7:31)
    - Doubling of f_u (12% healthy vs. 26% uremic)
- ↓ tissue binding ..... ↓ V_d
  - Displacement by 'endogenous uremic byproducts'?
  - Digoxin (*J Clin Pharmacol* 1974;14:525)
    - ↓ V_d digoxin by 30%-50%
- ↑ body water ..... ↑ V_d
  - Hydrophilic drugs (e.g., aminoglycosides)

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Effect of CKD on Renal Excretion

- Most intuitive
- As kidney function ↓, GFR ↓
- As GFR ↓, secretion ↓, renal CL ↓
  - Disproportionate reductions?
- Accumulation of drugs/metabolites
- Dose adjust renally cleared drugs in proportion to decline in kidney function
  - Increase dosing interval or decrease dose

Slide courtesy of Tom Nolin