Reverse Translational Assessment of CYP450- and OATP-Mediated Clearance in Chronic Kidney Disease: from Clinical Data to PBPK Modeling

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Session Description and Objectives

- Does chronic kidney disease (CKD) affect the drug disposition in other organs, in addition to the kidneys?
- Is there any general rule concerning the need to conduct clinical study?
- Mechanistic understanding by undertaking reverse translational studies?
- Systematically evaluate the CKD effect on individual elimination pathways
- CYP450s and OATPs in healthy and differing severity CKD patients
- PBPK modeling can be a useful tool to identify missing physiological parameters

Biography and Contact Information

- Ming-Liang Tan, Ph.D. Reviewer (Staff Fellow), Division of Quantitative Methods and Modeling, Office of Research and Standard, OGD/FDA
- Focus on advancing mechanistic based absorption PBPK modeling methods to establish bioequivalence in lieu of a study with clinical endpoints
- PBPK modeling and simulations to predict DDI, pharmacogenetics and renal impairment effect on pharmacokinetics
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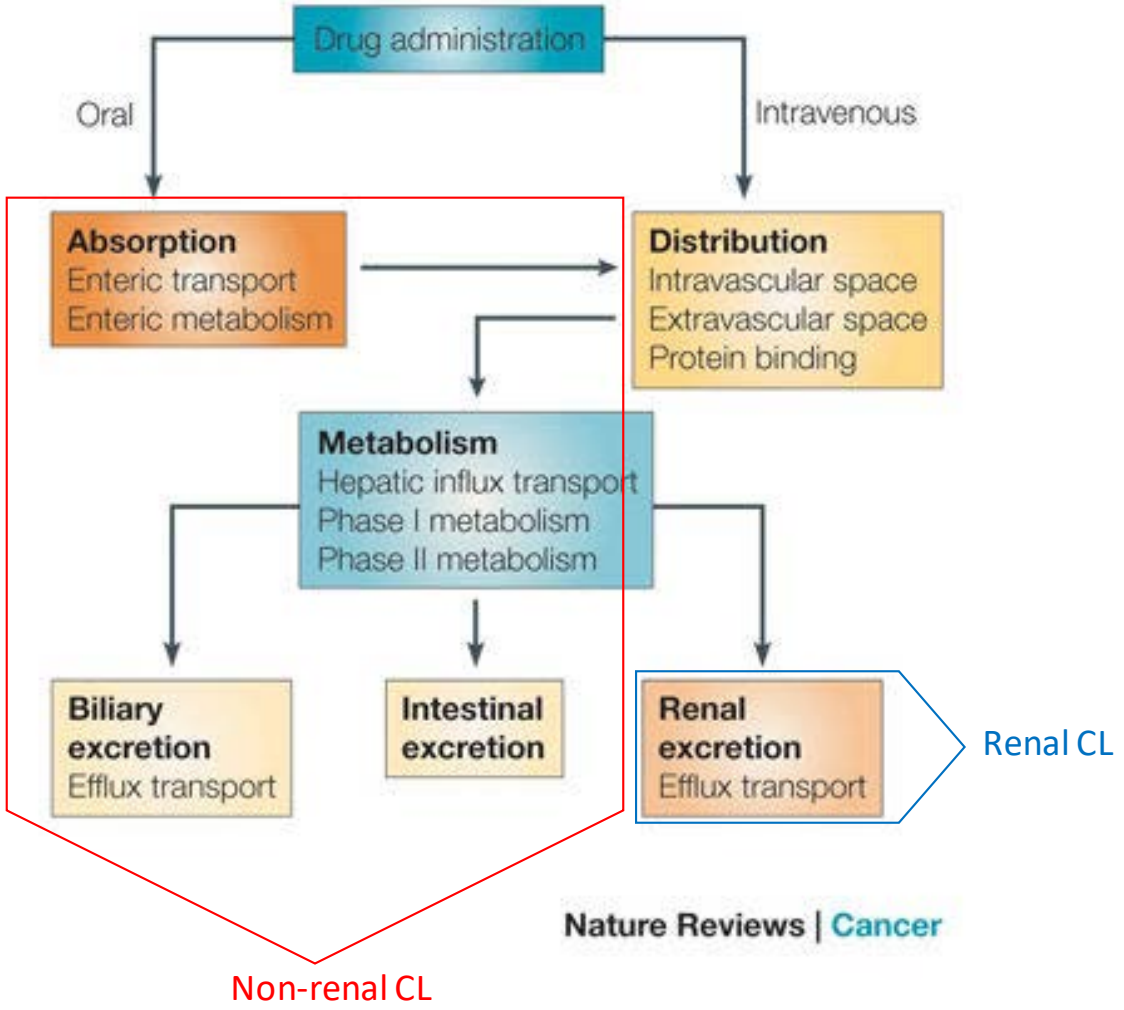
Why assess CKD effect on nonrenally cleared drugs?

- Continued growth of CKD population
- CKD alters the elimination of the drug in the kidneys
- CKD can also affect the disposition of nonrenally eliminated drugs
- Critical to assess CKD effect on nonrenal pathways, but complex and challenging due to inconsistent PK alterations observed.

Drug disposition and non-renal clearance

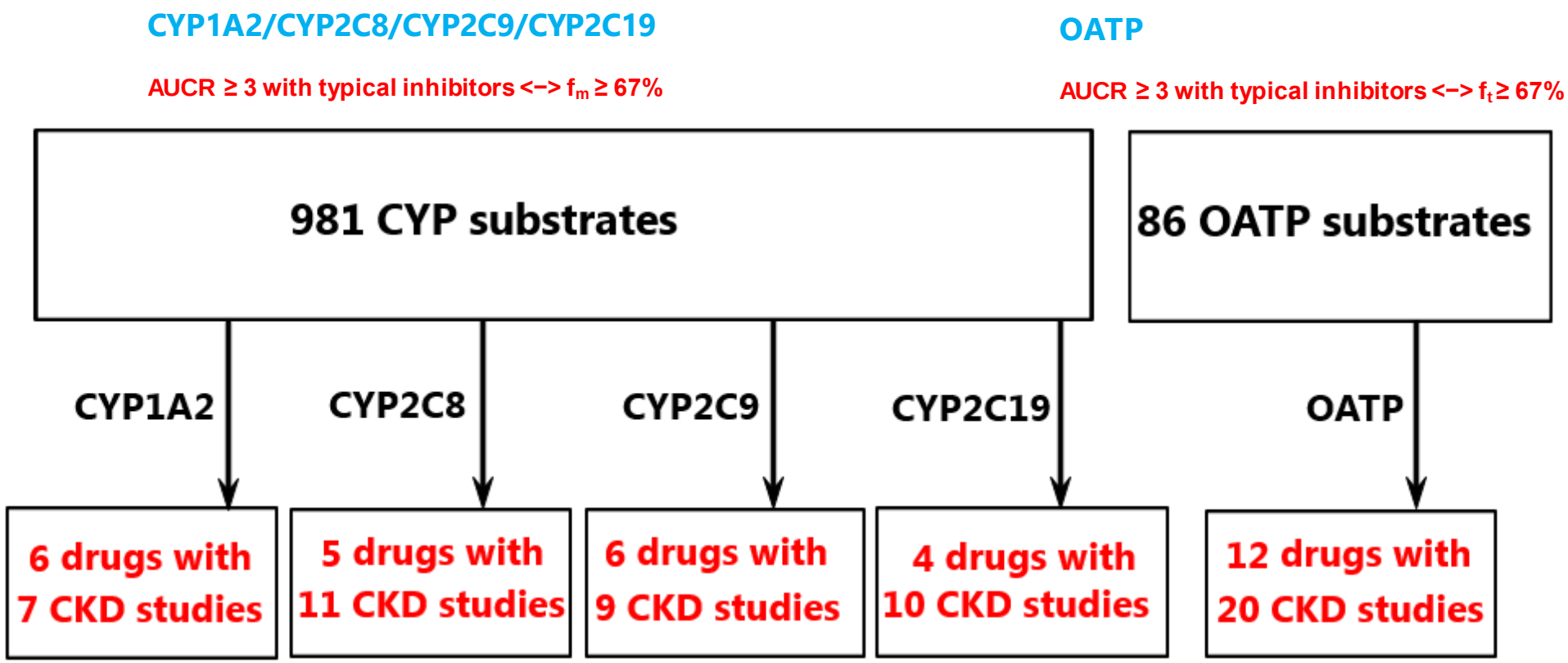


Undevia et al, *Nat. Rev. Cancer* 447, 5 (2005)

Outline

- Meta-analysis of CKD effect on nonrenal pathways
- Mechanistic understanding of CKD effect on nonrenal pathways
    1. Base PBPK model verification in healthy volunteers
    2. PBPK model application to CKD populations
        - CYP2C8 substrates
        - OATP substrate
        - CYP2C8/OATP dual substrate
- Conclusion

CKD Effect on Hepatic Pathways: Meta-analysis

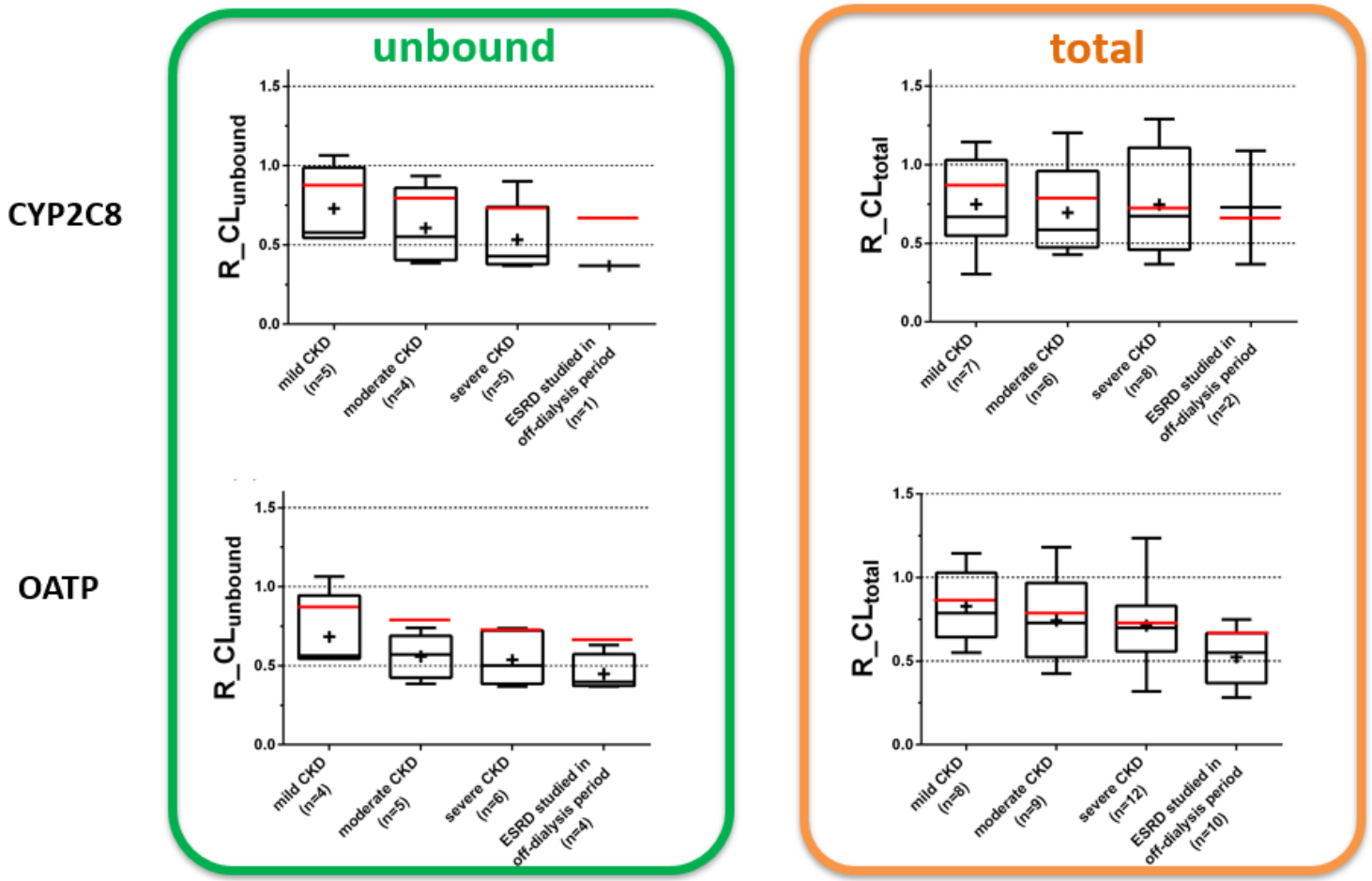


AUCR: AUC ratio; f_m=1-1/AUCR: fraction metabolized; f_t=1-1/AUCR for transporters.

Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 103, 854 (2018)

Effect of CKD on CYP2C8 and OATP

- ✓ CL ratio generally decreases as the CKD severity increases



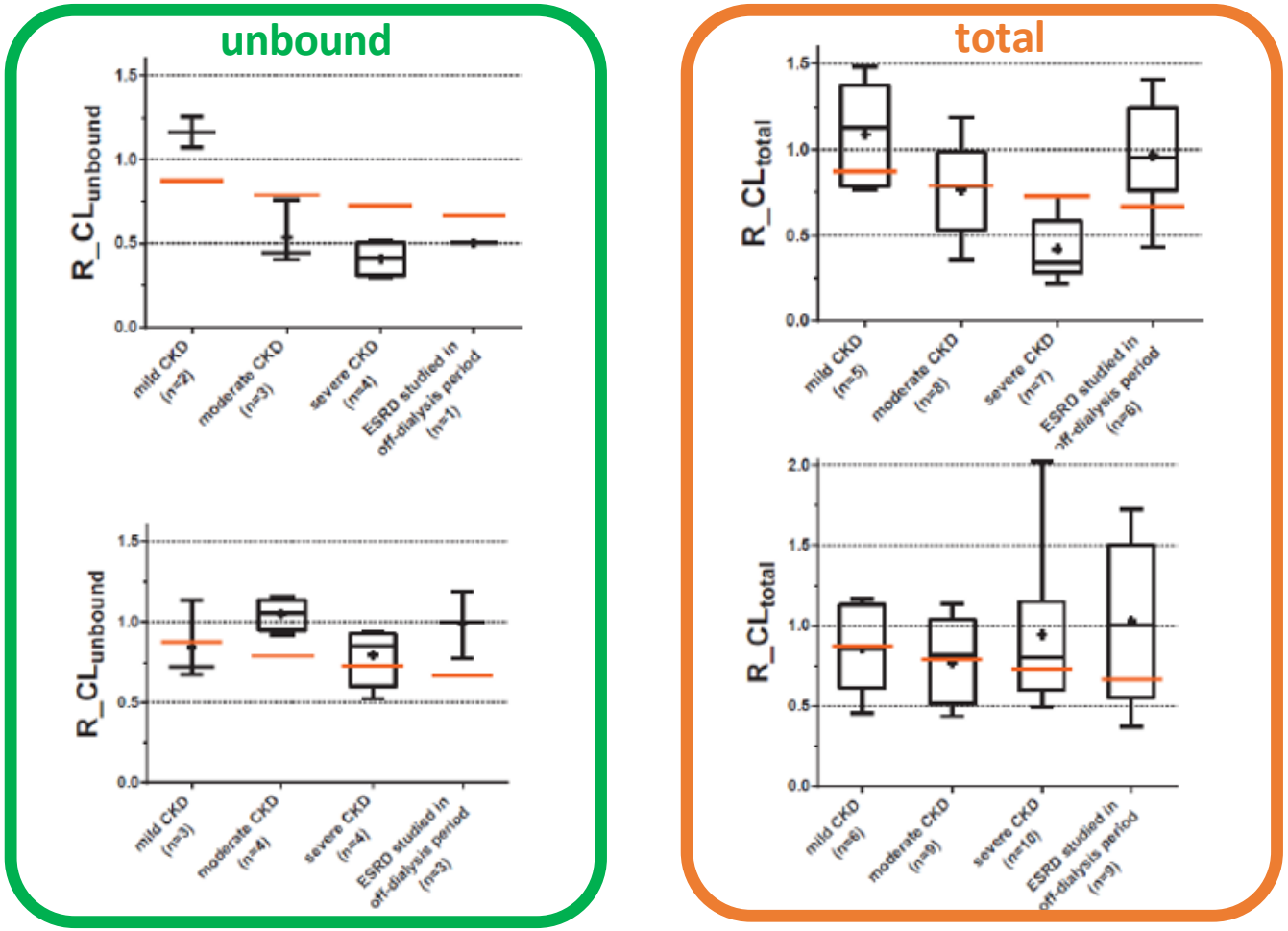
Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 103, 854 (2018)

Effect of CKD on CYP2D6 and CYP3A4/5

CL generally decreases for CYP2D6, while limited and variable effect for CYP3A4/5

CYP2D6

CYP3A4/5



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

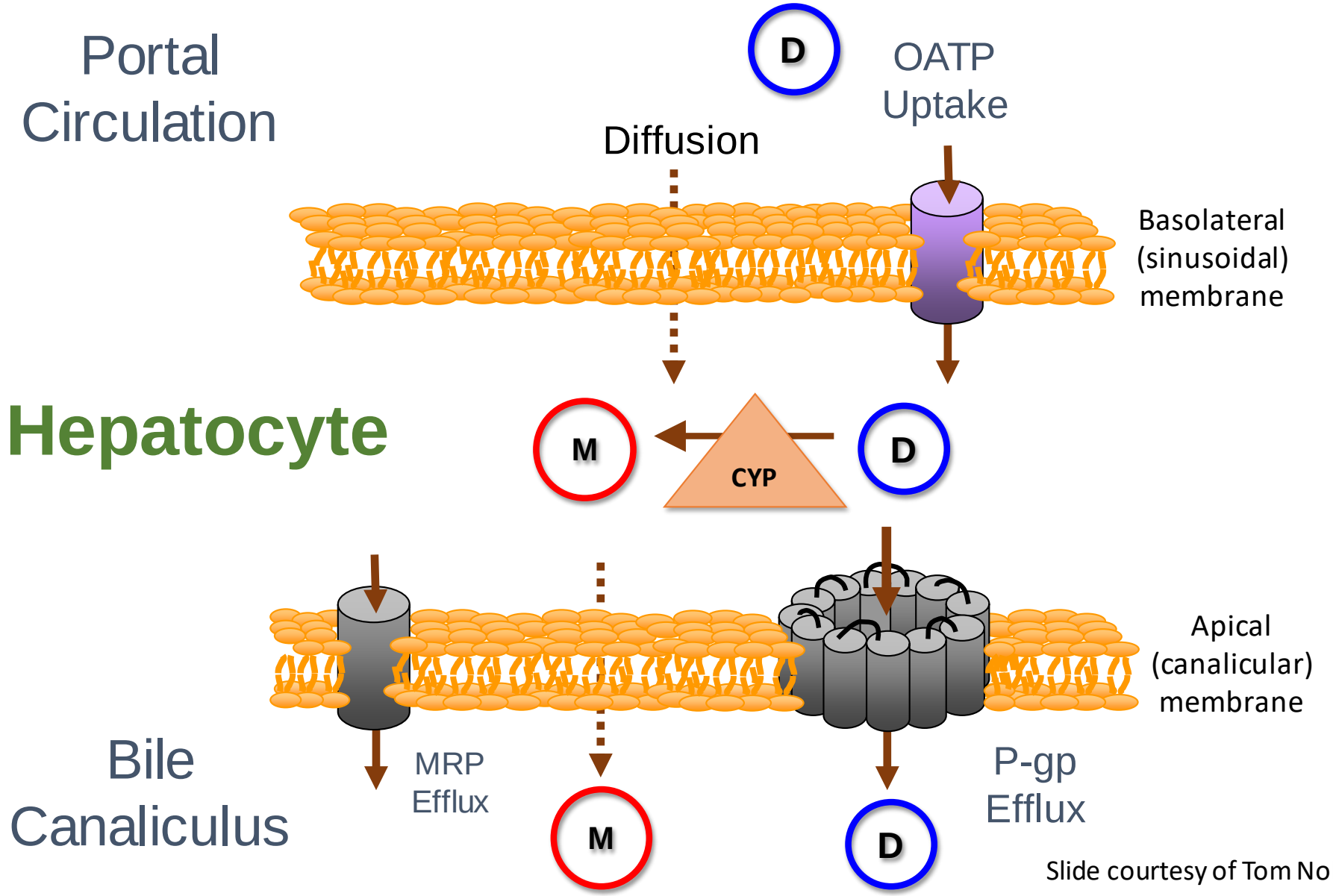
Effect of CKD on nonrenally eliminated pathways

PK of nonenally cleared drugs was affected differentially by CKD

- 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

Yoshida K *et al.*, *Clin. Pharmacol. Ther.* 100, 75 (2016)
Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 103, 854 (2018)

Overlapping Substrate Specificity

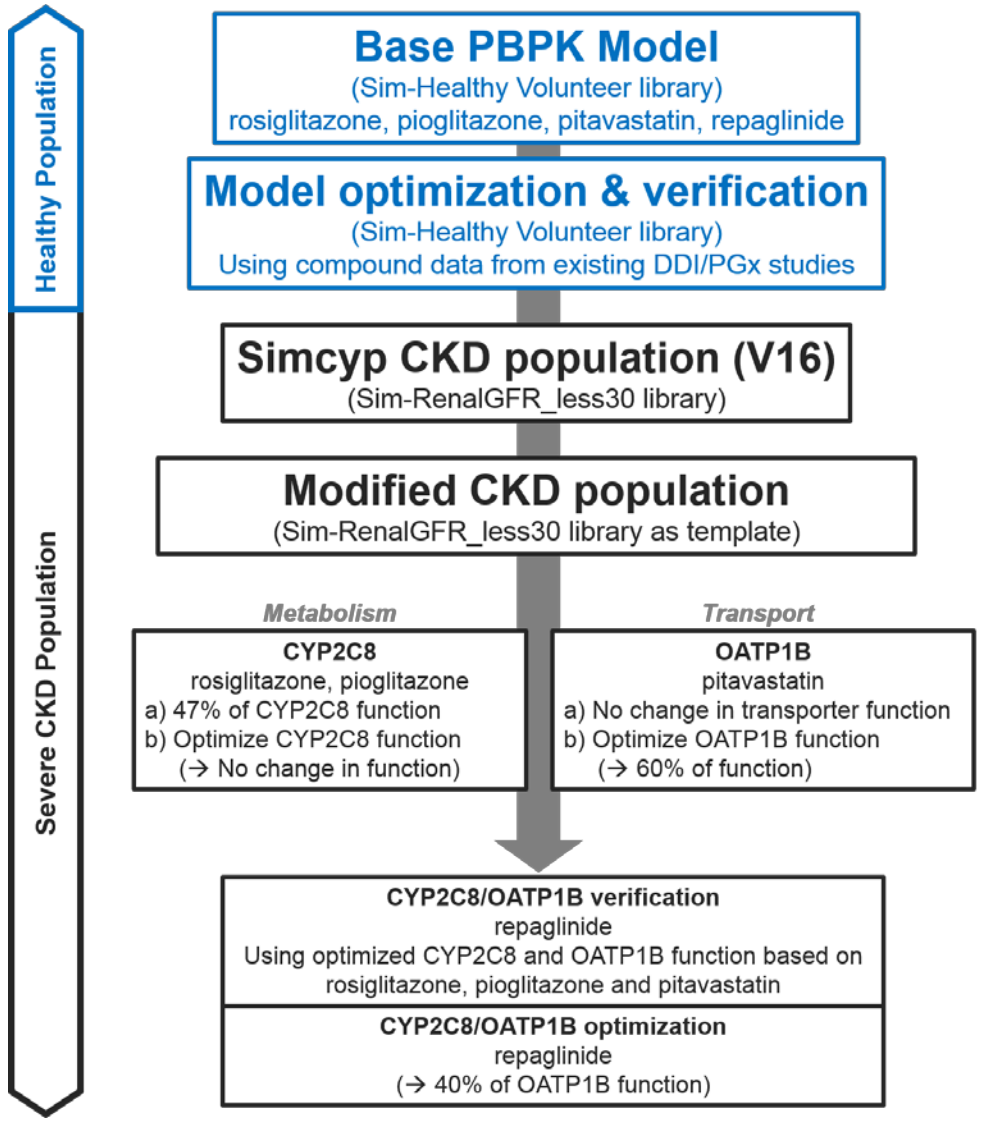


Slide courtesy of Tom Nolin, modified

Outline

- Meta-analysis of CKD effect on nonrenal pathways
- Mechanistic understanding of CKD effect on nonrenal pathways
  1. Base PBPK model verification in healthy volunteers
  2. PBPK model application to CKD populations
     - CYP2C8 substrates (rosiglitazone, pioglitazone)
     - OATP substrate (pitavastatin)
     - CYP2C8/OATP dual substrate (repaglinide)
- Conclusion

Workflow to predict drug PK in RI using PBPK



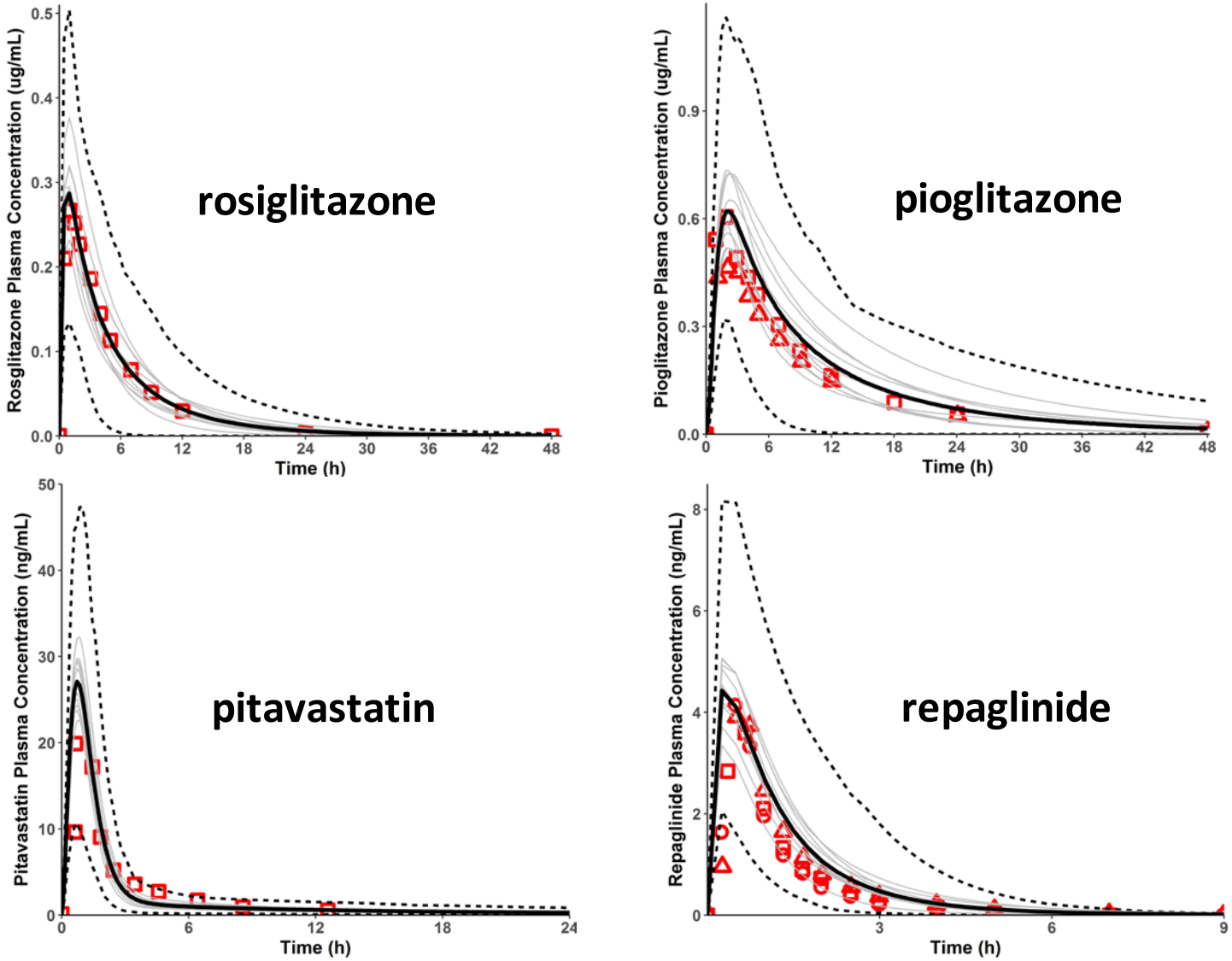
Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

PBPK base models

Parameters	Rosiglitazone	Pioglitazone	Pitavastatin	Repaglinide
Physicochemical properties				
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
Distribution				
Distribution model	Minimal PBPK	Minimal PBPK	Full PBPK	Full PBPK
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)	
$CL_{int,CYP3A4}$ (µl /min/mg protein)				38 (HLM)
$CL_{int,others}$ (µl/min/mg protein)			1453	
Renal clearance (l/h)	0.32	0	0.129	0
Hepatobiliary transport				
Passive diffusion (ml/min/10^6cells)			0.011	0.024
$CL_{int,active}$ (ml/min/10^6cells)			0.0584 (OATB1B1), 0.0051 (OATP1B3)	0.037 (OATP1B1)

Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

PBPK Model Verification in Healthy Volunteers



Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

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	3.22	1.19
Pitavastatin	*SLCO1B1* polymorphism (c. 521 CC vs c. 521 TT)	1.90	3.08	0.62
	Gemfibrozil	1.58	1.45	1.09
	Cyclosporine	2.84	4.55	0.62
Repaglinide	*SLCO1B1* polymorphism (c. 521 CC vs c. 521 TT)	1.88	1.83	0.97
	Gemfibrozil	3.22	5.0	0.64
	Cyclosporine	3.00	2.4	1.25

DDI: drug-drug interaction, PGx: pharmacogenetics

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

Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

System Parameters in Simcyp CKD Populations

Selected physiological and biochemical parameters in Simcyp V16

Parameters		HV	Severe CKD	$Ratio_{RI/Normal}$
2C8 (pmol/mg-protein)		24	11.3	0.47
2C9 (pmol/mg-protein)		73	34.5	0.47
2C19 (pmol/mg-protein)		14	6	0.43
3A4 (pmol/mg-protein)		137	87.3	0.64
OATP1B1 (pmol/10^6 hepatocytes)		4.28	4.28	1
OATP1B3 (pmol/10^6 hepatocytes)		4.3	4.3	1
HSA (g/l)	M	50.34	43.08	0.86
	F	49.38	37.8	0.77
Hematocrit (%)	M	43.0	33.2	0.77
	F	38.0	31.3	0.82
Gastric emptying time (h)		0.40	0.65	1.63

HSA: human serum albumin, HV: healthy volunteer

Simcyp Simulator (V16R1; Certara, UK)

CKD Effect on CYP2C8 Substrate Drugs

Substrate Drug	CKD populations	fu (%) HV	fu (%) CKD	AUCR (total) Simulated	AUCR (total) Observed	AUCR (total) R value	AUCR (unbound) Simulated	AUCR (unbound) Observed	AUCR (unbound) 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 severe CKD population

- 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.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

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
- OATP activity needs to be reduced to up to 60% in order to match the observed AUCR

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

Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

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
- Improved prediction when using OATP reduced to 60% from pitavastatin study
- OATP activity needs to be reduced to ~ 40% in order to match the observed AUCR

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

Tan M-L *et al.*, *Clin. Pharmacol. Ther.* 105, 719 (2019)

Conclusions

- CYP2D6 and OATP1B mediated drug CL generally ↓ as CKD severity ↑
- Limited effect on CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 mediated CL
- CYP enzyme and OATP1B transporter interplay can be understood by PBPK modeling:
  - ✓ Negligible reduction in CYP2C8 enzyme function required to match the AUC change for CYP2C8 substrates
  - ✓ Decreases in OATP activity of up to 60% needed to match the AUC change observed in severe CKD subjects.
- Reverse translational approach to identify missing physiological aspects based on the clinical data available, using PBPK modeling.

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Questions

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