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Physiologically-Based Pharmacokinetic Modelling of Creatinine-Drug Interactions in the Chronic Kidney Disease Population

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Elevated serum creatinine (S_{Cr}) caused by the inhibition of renal transporter(s) may be misinterpreted as kidney injury. The interpretation is more complicated in patients with chronic kidney disease (CKD) due to altered disposition of creatinine and renal transporter inhibitors. A clinical study was conducted in 17 patients with CKD (estimated glomerular filtration rate 15–59 mL/min/1.73 m^2); changes in S_{Cr} were monitored during trimethoprim treatment (100–200 mg/day), administered to prevent recurrent urinary infection, relative to the baseline level. Additional S_{Cr}-interaction data with trimethoprim, cimetidine, and famotidine in patients with CKD were collated from the literature. Our published physiologically-based creatinine model was extended to predict the effect of the CKD on S_{Cr} and creatinine-drug interaction. The creatinine-CKD model incorporated age/sex-related differences in creatinine synthesis, CKD-related glomerular filtration deterioration; change in transporter activity either proportional or disproportional to glomerular filtration rate (GFR) decline were explored. Optimized models successfully recovered baseline S_{Cr} from 64 patients with CKD (geometric mean fold-error of 1.1). Combined with pharmacokinetic models of inhibitors, the creatinine model was used to simulate transporter-mediated creatinine-drug interactions. Use of inhibitor unbound plasma concentrations resulted in 66% of simulated S_{Cr} interaction data within the prediction limits, with cimetidine interaction significantly underestimated. Assuming that transporter activity deteriorates disproportional to GFR decline resulted in higher predicted sensitivity to transporter inhibition in patients with CKD relative to healthy patients, consistent with sparse clinical data. For the first time, this novel modelling approach enables quantitative prediction of S_{Cr} in CKD and delineation of the effect of disease and renal transporter inhibition in this patient population.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Serum creatinine (S_{Cr}), the key endogenous biomarker of kidney function, increases due to inhibition of renal transporters even in the absence of kidney injury. Disposition of both creatinine and renal transporter inhibitors differs between healthy subjects and patients with chronic kidney disease (CKD). Physiologically-based pharmacokinetic (PBPK) models to simulate creatinine-drug interactions have previously only been reported for healthy populations.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Can PBPK modelling of creatinine predict the disease effect on S_{Cr} and creatinine-drug interactions in patients with CKD?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ A PBPK model that can account for disposition of creatinine and effects of renal transporter inhibitors in patients with CKD has been developed. The model can successfully simulate creatinine-drug interactions in this population.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ The developed model enables quantitative translation of renal transporter *in vitro* inhibition data together with disease-related changes to predict the extent of changes in S_{Cr} in patients with CKD.

Estimated glomerular filtration rate (eGFR) based on serum creatinine (S_{Cr}) is widely used clinically as an index of renal function.[1] However, inhibition of renal transporters leads to transient increase in S_{Cr} (creatinine-drug interaction) even in the absence of kidney injury,[2] because a certain proportion of creatinine is eliminated by active secretion via renal transporters.[3,4] Therefore, a method that can identify the cause of increased S_{Cr} would be useful in clinical practice.

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Received: June 12, 2020; accepted: October 1, 2020. doi:10.1002/psp4.12566

Chronic kidney disease (CKD) is often associated with progressive renal dysfunction, characterized by increased S_{Cr}.[1] In addition to gradual decline in glomerular filtration rate (GFR), patients with CKD show several physiological changes in the kidneys and other organs that can affect elimination of drugs/endogenous substances. These include accumulation of uremic solutes,[5,6] reduced serum albumin concentration,[7] metabolic acidosis,[8,9] and reduced expression/activity of metabolizing enzymes and transporters in the liver.[10] These physiological changes in CKD can affect the disposition of both creatinine and drugs that inhibit renal transporters.

A number of clinical analyses assumed that tubular secretion of solutes decreases in CKD in proportion to GFR ("intact nephron hypothesis" (INH)[11]).[5,6] In contrast, other studies reported changes in tubular secretion (e.g., via organic anion transporters (OATs)) that were inconsistent with GFR.[5,6,12] In the case of creatinine, smaller extent of decline in tubular secretion relative to GFR was implied because of reported increase in ratio of creatinine clearance to GFR (C_{Cr}/GFR) in patients with CKD.[3,4] Moreover, the C_{Cr}/GFR in patients with CKD approached the level of healthy subjects after administration of cimetidine (renal transporter inhibitor).[13] Therefore, a higher degree of creatinine-drug interaction may occur in the CKD population than in subjects with normal renal function (assuming equal dosing) due to combination of (i) higher exposure of inhibitor drug due to lower impaired hepatic and/or renal elimination, and (ii) decline in transporter activity disproportionate to GFR (higher C_{Cr}/GFR ratio in patients with CKD relative to healthy).
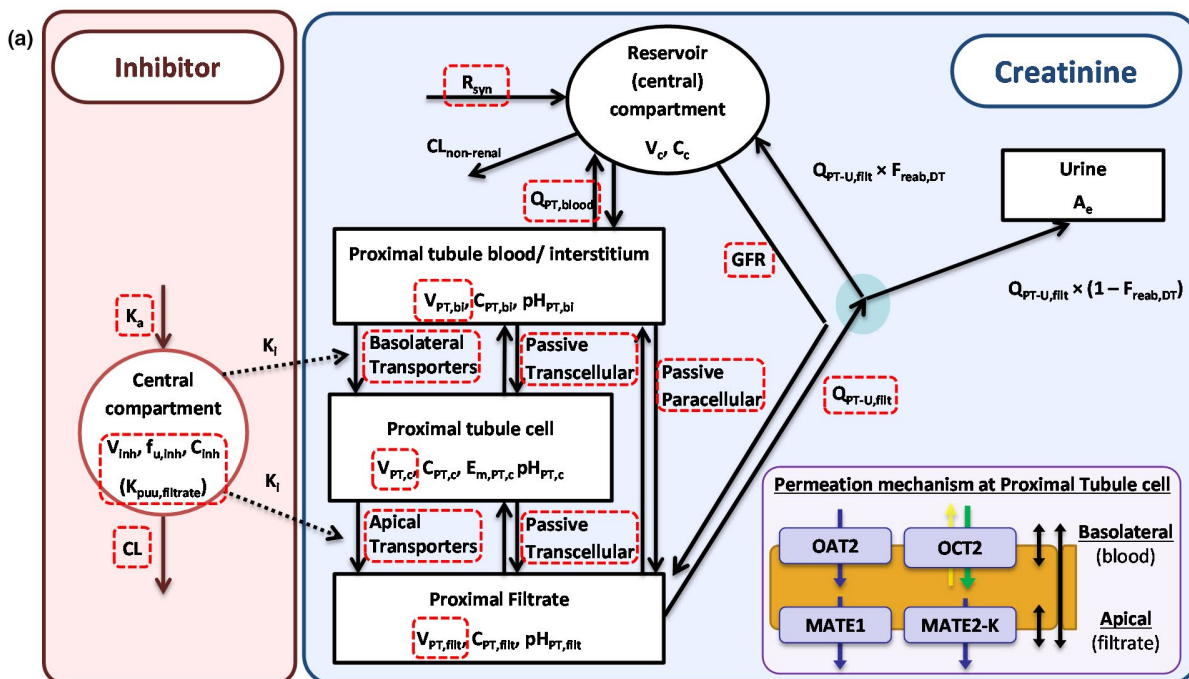
Physiologically-based pharmacokinetic modelling has been applied to predict the effect of CKD on drug exposure.[14–17] In the case of creatinine, several models have been reported and applied to simulate creatinine-drug interactions in healthy subjects.[18–21] However, there is currently no model in place to capture CKD-related changes in creatinine renal disposition. Our recently published physiologically-based creatinine model, developed for healthy subjects, accounted for multiple transporters involved in renal creatinine elimination, assuming either unidirectional or bidirectional transport via organic cation transporter (OCT) 2 (uptake-OCT2 or bidirectional-OCT2 model), driven by an electrochemical gradient (**Figure 1a**).[20,21] In addition, the models incorporated endogenous creatinine synthesis, glomerular filtration, and passive diffusion across proximal tubule cells. The models, initially based on proteomics-informed *in vitro-in vivo* extrapolation of transporter kinetics, were optimized by creatinine-trimethoprim interaction data and successfully simulated the percent change in S_{Cr} (%ΔS_{Cr}) postdosing of 11 further inhibitors.

This study aimed to extend the existing creatinine model to the CKD population by accounting for physiological changes associated with the disease and to predict creatinine-drug interactions in these patients for inhibitors of OCT2 and multidrug and toxin extrusion protein (MATE) transporters. Literature data were collated based on availability of both clinical pharmacokinetics (PKs) for the inhibitor, and interaction data in patients with moderate (G3; eGFR 15–29 mL/min/1.73 m^2) to severe (G4, eGFR 30–59 mL/min/1.73 m^2) CKD. In addition, a new clinical study was conducted in 17 patients with moderate-to-severe CKD and their S_{Cr} was monitored during prophylactic trimethoprim treatment (100–200 mg/day). The creatinine-CKD models were developed and evaluated in a stepwise manner (**Figure 1b**):

1. Modification of the creatinine models and corresponding system parameters to account for physiological changes in CKD and model verification against independent clinical dataset.
2. Development of PK models for different inhibitors using reported plasma concentration-time profiles in patients with CKD.
3. Simulation of creatinine-drug interactions in patients with CKD and evaluation of predicted %ΔS_{Cr} against clinical observations.

Figure 1 Model optimization for creatinine-drug interaction in patients with chronic kidney disease (CKD). (**a**) A reprinted model structure from the previous study showing the creatinine models for healthy subjects.[20,21] Permeation mechanisms at proximal tubule cell in two creatinine models with different description of organic cation transporter (OCT) 2 were presented in purple shaded area: uptake-OCT2 model (green arrow only) and bidirectional-OCT2 model (both green and yellow arrows). See Scotcher *et al.*[20,21] regarding details of the models and system parameters. Parameters optimized for patients with CKD in this study were enclosed by red dashed squares. (**b**) Strategy of model optimization. The simulation of creatinine-drug interaction in patients with CKD was implemented in three steps; (1) optimization of creatinine model for patients with CKD, (2) development of inhibitors' pharmacokinetic (PK) models for patients with CKD, and (3) simulation of creatinine-drug interaction in patients with CKD. In step 1, both uptake-OCT2 and bidirectional-OCT2 models optimized for healthy subjects (step 1-0) were extended for patients with CKD in four sub-steps. In step 1-1, estimated glomerular filtration rate of CKD patient i ($eGFR_i$) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1] (**Eq. S1**), where $S_{Cr,i}$ and Age_i represent serum creatinine (S_{Cr}) and age of CKD patient i, $a = -0.329$ and $k = 0.7$ for women, and $a = -0.411$ and $k = 0.9$ for men, *min* and *max* indicate the minimum of S_{Cr}/k or 1, or maximum of S_{Cr}/k or 1, respectively. In step 1-2, creatinine synthesis rate of CKD patient i ($R_{syn,i}$) was calculated using the reported regression equation[22] (**Eq. S5**), with correction using the calculated body surface area. WT_i represents body weight of CKD patient i, C0 = 27 and C1 = 0.173 for men, and C0 = 25 and C1 = 0.175 for women. In step 1-3, a value of parameter j in the proximal or distal tubule of CKD patient i ($SysPara(j)_{CKD,i}$) was altered in proportion to glomerular filtration rate (GFR; **Eq. S6**, intact nephron hypothesis (INH)), where *Sys Para(j)$_{healthy}$* represents a representative value of system parameter j in healthy subjects, $GFR_{CKD,i}$ and $GFR_{healthy}$ are GFR in CKD patient i and a healthy subject (125 mL/min), respectively. Abbreviations of optimized parameters are listed in **Table 2**. In step 1-4, clearances of renal transporters were altered disproportional to GFR (non-INH scenario). Relative change in intrinsic clearance (*CLint*) of organic anion transporter (OAT) 2 in CKD patient i ($CLint(OAT2)_{CKD,i}/CLint(OAT2)_{healthy}$) was calculated as a function of relative change in GFR ($GFR_{CKD,i}/GFR_{healthy}$) and additional deterioration of OAT2 clearance beyond INH ($Fx_{OAT2,i}$; **Eqs. S9,S10**). Relative change in clearances of OCT2 and multidrug and toxin extrusion protein (MATE) transporters in CKD patient i (*expressed as CLint(j)$_{CKD,i}$/CLint(j)$_{healthy}$* where $CLint(j)_{CKD,i}$ and *CLint(j)$_{healthy}$* represent *CLint* of transporter j in representative populations) were estimated as a linear function of GFR, where $Coeff_{CKD,TP}$ represents the slope of the linear function (**Eq. S11**). Combined with PK models for inhibitors developed in step 2, the creatinine models were used to simulate creatinine-drug interaction in CKD population in step 3.

(a)

Inhibitor

Creatinine

R_{syn}

Reservoir (central) compartment V_c, C_c

$CL_{non-renal}$

$Q_{PT,blood}$

Urine A_e

$Q_{PT-U,filt} \times F_{reab,DT}$

Proximal tubule blood/ interstitium

$V_{PT,bi}$, $C_{PT,bi}$, $pH_{PT,bi}$

GFR

$Q_{PT-U,filt} \times (1 - F_{reab,DT})$

K_a

Basolateral Transporters

Passive Transcellular

Passive Paracellular

Central compartment

V_{inh}, $f_{u,inh}$, C_{inh}

($K_{puu,filtrate}$)

K_i

K_i

Proximal tubule cell

$V_{PT,c}$, $C_{PT,c}$, $E_{m,PT,c}$ $pH_{PT,c}$

$Q_{PT-U,filt}$

CL

Apical Transporters

Passive Transcellular

Proximal Filtrate

$V_{PT,filt}$, $C_{PT,filt}$, $pH_{PT,filt}$

Permeation mechanism at Proximal Tubule cell

OAT2 | OCT2 — Basolateral (blood)

MATE1 | MATE2-K — Apical (filtrate)

(b)

(1) Optimization of creatinine model for CKD

0. Default creatinine models
- Uptake- or bidirectional-OCT2 model optimized for healthy subjects

1. Glomerular filtration rate
- Individual *eGFR* calculated using CKD-EPI equation and S_{Cr} (Eq. S1)

$$eGFR_i = 141 * \min(\frac{S_{Cr,i}}{k}, 1)^a * 141 * \max(\frac{S_{Cr,i}}{k}, 1)^{-1.209} * 0.993^{Age,i} * 1.018[\text{if female}] * 1.018[\text{if black}]$$

2. Creatinine synthesis rate (R_{syn})
- Individual R_{syn} calculated using the regression equation (Eq. S5)

$$R_{SYN,i} = (C0 - (C1 * Age_i)) * WT_i / 24$$

3. Intact nephron hypothesis
- Decreased system parameters in the proximal tubule proportional to GFR (Eq. S6):
$V_{PT,bi}$, $V_{PT,cell}$, $V_{PT,filt}$, $Q_{PT-U,filt}$, $CL_{PD,trans}$, $CL_{PD,para}$, ($CL_{int,transporter}$ in INH scenario)

$$SysPara(j)_{CKD,i} = \frac{GFR_{CKD,i}}{GFR_{healthy}} * SysPara(j)_{healthy}$$

4. Transporter clearance (Non-INH scenario)
- Deterioration of OAT2 clearance beyond INH (Eq. S10)

$$\frac{CLint(OAT2)_{CKD,i}}{CLint(OAT2)_{healhty}} = \frac{GFR_{CKD,i}}{GFR_{healthy}} * Fx_{OAT2,i}$$

- Relative change in clearances of OCT2 and MATE transporters (Eq. S11)

$$\frac{CLint(j)_{CKD,i}}{CLint(j)_{healhty}} = Coeff_{CKD,TP} * \left(\frac{GFR_{CKD,i}}{GFR_{healthy}} - 1\right) + 1$$

Validation of creatinine model; Predictability of baseline S_{Cr}
- Dataset for model development; baseline S_{Cr} form eight clinical studies, 64 patients in CKD G3-4
- Additional model validation using external dataset

(2) Development of inhibitors' PK models for CKD
- Compartment models of trimethoprim, cimetidine, and famotidine optimized for plasma PK profile in CKD patients
- Plasma protein binging in CKD patients

(3) Simulation of creatinine-drug interaction in CKD
- Twelve study groups, 90 patients in CKD G3-4
- Use of novel prediction limits considering intra-individual variability in baseline S_{Cr}

METHODS

Collation of clinical data in patients with CKD

Clinical creatinine-drug interaction data were obtained from a new clinical study and the existing literature. The Salford Kidney Study is a large longitudinal CKD cohort investigation conducted with > 3,000 patients with non-dialysis CKD, recruited during the period 2002–2015 in Salford Royal NHS Service Foundation Trust (**Supplementary Material Section S1**). From the entire cohort, data from 17 patients with CKD (6 men and 11 women, age 22–88 years, stage G3–4) were included for evaluation of the creatinine-trimethoprim interaction. Subjects on any additional comedications known to cause creatinine-drug interaction in healthy subjects[21] were excluded. Trimethoprim treatment was usually for prophylaxis against recurrent urinary infection (100–200 mg/day), lasting on average 91 days (ranging from 10–420 days). Patients' S_{Cr} at the baseline ($S_{Cr,baseline}$) were defined as the mean of measurements in the period up to 1,000 days prior to initiation of trimethoprim; "day 1" was the first S_{Cr} measurement after initiation of trimethoprim treatment. The %ΔS_{Cr} was calculated as percent change from $S_{Cr,baseline}$ to the S_{Cr} at day 1. S_{Cr} values after day 1 were excluded due to potential confounding factors (e.g., deterioration of CKD or adaptation to trimethoprim treatment).

Literature clinical creatinine-drug interaction data were collated for 15 renal transporter inhibitors that were evaluated with the existing creatinine model for healthy subjects in our previous study (**Table S3**).[21] Inclusion criteria for clinical studies are detailed in the **Supplementary Material Section S2**. Reported C_{Cr}/GFR ratio data in healthy and CKD populations were collated (see **Supplementary Material Section S3**). Mean values and standard deviations (SD) of C_{Cr}/GFR were calculated for each CKD group accounting for the number of subjects in each study.

Simulation of creatinine-drug interaction in patients with CKD

Simulations of creatinine-drug interaction were implemented in three steps: (i) optimization of creatinine CKD models, (ii) development of PK models for each inhibitor, and (iii) simulation of the creatinine-drug interaction in patients with CKD (**Figure 1b**). Uptake-OCT2 or bidirectional-OCT2 models were optimized independently.

Optimization of creatinine models for CKD. Creatinine CKD models were developed in a stepwise manner. GFR parameter was informed by either (i) gold-standard exogenous markers (e.g., inulin and iothalamate), or, when such measurements were not available, (ii) eGFR based on measured S_{Cr} and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1], which was validated against S_{Cr} and iothalamate renal clearance in patients with CKD (**Eq. S1**). Endogenous creatinine synthesis rate (R_{SYN}) was calculated using a published regression equation[22] using demographic data (age, sex, and weight (WT); **Eq. S5**). Renal blood flow was decreased by 27% and 42% in CKD G3 and G4 relative to healthy subjects, respectively, based on magnetic resonance imaging.[23] The volume of distribution in the central compartment was assumed to be the same as in healthy subjects, as CKD has minimal effect on total body water.[24] Values of pH and membrane potential in the proximal tubule, were assumed the same as in healthy populations due to the scarcity of information in the CKD population.

Parameters relevant to proximal and distal tubule, such as passive membrane permeability (CL_{PD}), volumes of proximal tubule compartments, and filtrate flow rate (Q_{U-filt}), were decreased proportionally to GFR (**Eq. S6**), in line with INH. Modification of Q_{U-filt} was based on the assumption that flow out of the proximal tubular filtrate changed in proportion to GFR; changes in CL_{PD} were attributed to decreased membrane surface area of proximal and distal tubule in CKD. CKD-dependent change in filtrate pH was assumed to have minimal effect on creatinine CL_{PD}, supported by our previous study.[9] These assumptions for CL_{PD} and Q_{U-filt} resulted in the same creatinine fraction reabsorbed in the distal tubule in healthy patients and patients with CKD (**Eqs. S7,S8**). Absolute amount of water reabsorbed in distal tubule was reduced as per INH.

Two scenarios were investigated in creatinine CKD model with respect to transporter clearance parameters: (i) activity of all transporters decreased proportionally to GFR (**Eq. S6**, "INH scenario") or (ii) change in transporter activity was disproportionate to GFR, supported by higher C_{Cr}/GFR ratio in CKD relative to healthy ("non-INH scenario"). Deterioration of OAT2 activity in CKD was based on the analysis of clinical data for OAT2 substrates[12] (**Eqs. S9,S10**). Relative change in clearances of other transporters in CKD were expressed as a linear function of GFR (**Eq. S11**), and slope of the function ($Coeff_{CKD,TP}$) were estimated for uptake-OCT2 or bidirectional-OCT2 models independently by fitting the models to overall means of C_{Cr}/GFR in CKD and healthy populations using the lsqnonlin function in Matlab (R2017a; MathsWorks). The same $Coeff_{CKD,TP}$ value was assumed for OCT2 and MATE transporters. Sensitivity of the creatinine CKD models to the uncertainty in system parameters or degree of transporter inhibition is shown in **Supplementary Material Section S5**.

Development of PK models for the inhibitors in patients with CKD. One-compartment or two-compartment PK models were developed for trimethoprim, cimetidine, and famotidine (details in **Supplementary Material Section S6**). As there was no clear relationship between exposure of the inhibitors and CKD stage in our scarce dataset, PK models were developed by simultaneous fitting of all available plasma concentration-time profiles in patients with CKD G3–4. One-compartment model for trimethoprim was developed in NONMEM version 7.42 using WT as a covariate. Models for cimetidine and famotidine were based on mean PK profiles using the naïve pooled method.

Simulation of creatinine-drug interaction in patients with CKD. Simulation of creatinine-drug interactions was performed by combining the creatinine and inhibitor models for patients with CKD. Inhibitory effect on intrinsic clearances of individual transporters was simulated as described previously[21,25] (**Supplementary Material Section S7**).

Verification of creatinine CKD model

The predictability of the creatinine models was evaluated with $S_{Cr,baseline}$ and $\%\Delta S_{Cr}$ as end points. The predictability of $S_{Cr,baseline}$ was assessed by comparing the observed and predicted values, quantified by geometric mean fold-error (gmfe; Eq. 1),[26] and percentage of simulated data within 1.2-fold of observed values. Acceptable creatinine models were selected based on gmfe < 1.15 and recovery of reported C_{Cr}/GFR. The predictability of $S_{Cr,baseline}$ was also evaluated using independent external dataset (**Supplementary Material Section S8**).

$$\text{gmfe} = 10^{\frac{1}{n} \sum \left| \log_{10} \left(\frac{S_{Cr,baseline,predicted}}{S_{Cr,baseline,observed}} \right) \right|} \quad (1)$$

The predictability of $\%\Delta S_{Cr}$ was evaluated by comparing means of observed and predicted $\%\Delta S_{Cr}$ for each study using mean absolute-error (Eq. 2). In addition, prediction performance of $\%\Delta S_{Cr}$ was evaluated using novel prediction limits that accounted for intra-individual variability in $S_{Cr,baseline}$ in patients with CKD; these boundaries are much stricter than conventional twofold (details in **Supplementary Material Section S9**).[21,27] When data on timing of blood sampling for S_{Cr} was missing, the maximum predicted $\%\Delta S_{Cr}$ during the potential sampling period was used.

$$\text{MAE} = \frac{1}{n} \sum \left| \%\Delta S_{Cr,predicted} - \%\Delta S_{Cr,observed} \right| \quad (2)$$

RESULTS

Analysis of creatinine data in patients with CKD

In the Salford Kidney Study, S_{Cr} at baseline and post-trimethoprim were evaluated in 17 patients with CKD G3 (n = 12) and G4 (n = 5) (**Table S1**). Trimethoprim caused a statistically significant increase in S_{Cr} from the mean value of 1.7 mg/dL at baseline (1.1–3.2 mg/dL) to 2.0 mg/dL (1.2–3.1 mg/dL) 91 days post-trimethoprim (mixed effects model, *P* < 0.01; **Figure 2a**, **Table S2**). Mean $\%\Delta S_{Cr}$ post-trimethoprim was 20% higher relative to the baseline (ranged from –12 to 86%), with no direct correlation between eGFR and $\%\Delta S_{Cr}$ (**Figure 2b**). The intra-individual coefficient of variability of $S_{Cr,baseline}$ was 8.9 ± 4.9%, which was higher than the reported value in healthy subjects (4.7%).[28]

A literature search identified 15 clinical studies evaluating either $S_{Cr,baseline}$ or $\%\Delta S_{Cr}$ in patients with CKD for three inhibitors of renal transporters (trimethoprim, cimetidine, and famotidine) that met inclusion criteria for the current analysis (**Table 1**). Data on $\%\Delta S_{Cr}$ in healthy patients and patients with CKD from the literature and the Salford Kidney Study were analyzed with respect to the daily dose of inhibitors (**Table S4**, **Figure S2**). Despite the lower daily doses in patients with CKD relative to healthy subjects, maximum mean $\%\Delta S_{Cr}$ across the studies was ~ 30% in both populations following administration of trimethoprim (13–31% in healthy patients and 7–33% in patients with CKD) and cimetidine (14–26% in healthy patients and 10–31% in patients with CKD). Although mean $\%\Delta S_{Cr}$ in patients with CKD tended to be higher than in healthy subjects when comparing the effects of trimethoprim of < 400 mg/day, the trend was inconclusive due to sparse and variable data.

Optimization of creatinine models for patients with CKD

The creatinine models were optimized to capture reported $S_{Cr,baseline}$ (1.1 to 3.9 mg/dL) in 64 patients with CKD (35 with G3 and 29 with G4, 31 men and 33 women, ages 22–88 years) from 8 clinical studies (**Table 1**). Initial application of the creatinine models[20,21] based on population
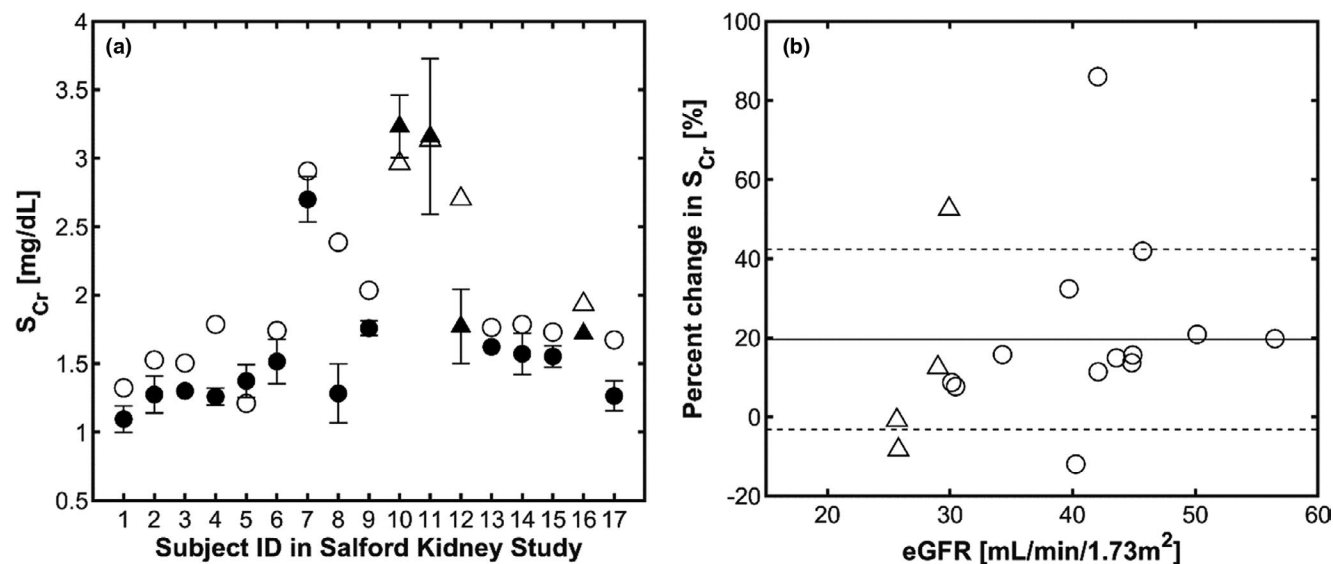

Figure 2 Evaluation of creatinine-drug interaction in Salford Kidney Study. (**a**) Serum creatinine (S_{Cr}) at baseline and post trimethoprim of 17 patients with chronic kidney disease (CKD) in Salford Kidney Study. Filled symbols and error bars represent means and standard deviations of S_{Cr} at the baseline (–1,000 day to last blood test prior to trimethoprim) in each patient; Open symbols represent S_{Cr} at the first test post trimethoprim (day 1); Circles: CKD G3 (estimate glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m²); Triangles: CKD G4 (eGFR 15–29 mL/min/1.73 m²). (**b**) Percent change in S_{Cr} post trimethoprim plotted against eGFR in Salford kidney study. Each symbol represents an individual patient with CKD; symbols for CKD stage, as described in **a**). Solid line and dashed lines represent mean and mean ± SD of percent change in S_{Cr} of all patients with CKD, respectively.

Table 1 Summary of clinical studies evaluating creatinine–drug interaction in patients with CKD

Inhibitor	Clinical study	Subject information (M; male, F; Female)	GFR, mL/min/1.73 m^2	Study design	Blood sampling for S_{Cr} post inhibitor	% change in S_{Cr}, mean ± SD	Individual's baseline S_{Cr}
Trimethoprim	Salford study group 1	n = 13, M3 F10, 25–79 years	26–56	100 mg q.d. oral	>Day 10, 12 hours after last dose	23 ± 25	Yes
	Salford study group 2	n = 4, M3 F1, 22–88 years	26–43	200 mg q.d. oral	>Day 10, 12 hours after last dose	9 ± 10	Yes
	Myre et al. (1987)[38]	n = 5, M2 F3, 37–57 years	15–23	100 mg b.i.d. oral	Day 10, 2–4 hours after morning dose	33 ± 26	Yes
	Tasker et al. (1975)[45] group 1[a]	n = 6, M5 F1, 34–80 years	27–47	160 mg b.i.d. oral	Days 6–10	28 ± 34	Yes
	Tasker et al. (1975)[45] group 2[b]	n = 4, M0 F4, 47–78 years	22–23	160 mg b.i.d. oral (days 1–3), q.d. oral (day 4–)	Days 6–10	7 ± 20	Yes
	Rieder et al. (1974)[30]	n = 9, M4 F5, 25–69 years	17–56	-	-	-	Yes
Cimetidine	Larsson et al. (1980)[46] group 1[c]	n = 8, 29–77 years	21–40	200 mg q.d. oral	Day 7	25	No[e]
	Larsson et al. (1980)[46] group 2[e]	n = 9, 29–77 years	36–55	(200 mg × 3 + 400 mg) per day oral	Day 7	31	No[e]
	Ishigami et al. (1989)[39]	n = 8, M7 F1, 28–67 years	16–29	400 mg b.i.d. oral	Day 7	12	No[e]
	Hilbrands et al. (1991)[47]	n = 5, 25–66 years	20–40	(400 mg × 2 + 600 mg) per day oral	Steady-state	26 ± 14	No[e]
	Ma et al. (1978)[31]	n = 8, M8 F0, 34–66 years	18–57	300 mg SD intravenous	24–48 hours after dose	10 ± 10	No[e]
	Larsson et al. (1981)[32]	n = 17, M12 F5, 31–68 years	19–60	-	-	-	Yes
	Bjaeldager et al. (1980)[48]	n = 6, M2 F4, 39–65 years	23–41	-	-	-	Yes
Famotidine	Ishigami et al. (1989)[39]	n = 8, M7 F1, 28–67 years	16–29	20 mg b.i.d. oral	Day 7	7	No[e]
	Abraham et al. (1987)[34]	n = 12, M10 F2, 28–54 years	10–41	10 mg SD intravenous	0–4 hours after dose	0	No[e]

CKD, chronic kidney disease; GFR, glomerular filtration rate; S_{Cr}, serum creatinine; SD, single dosing.
[a]Group with creatinine clearance above 25 mL/min.
[b]Group with creatinine clearance 15–25 mL/min.
[c]Group with creatinine clearance of 30–50 mL/min.
[d]Group with creatinine clearance of 50–75 mL/min.
[e]Excluded from the evaluation of baseline S_{Cr} due to lack of individual's S_{Cr}. Ma et al. (1978)[31] was not used for the evaluation of baseline S_{Cr} because individual's age was missing.

Table 2 System parameters in creatinine models optimized for patients with CKD

Parameter	Unit	Description	Optimization for CKD	Value in healthy[a,c] (GFR = 125 mL/min)	Value in CKD (GFR = 15 mL/min)[b,c]	
					INH scenario[d]	Non-INH scenario[d]
GFR	L/h	Glomerular filtration rate	eGFR calculated using CKD-EPI equation[1] (Eqs. S1,S2)	7.5		0.9
$Q_{PT,blood}$	L/h	Blood flow rate to proximal tubule	Percent reduction in renal blood flow in CKD relative to healthy[23]	58		34
R_{SYN}	mg/h	Endogenous creatinine synthesis rate	Calculated using the equation from Bjornsson et al. (Eq. S5)[22]	71		46
$V_{PT,bi}$	L	Volume of water in blood and interstitial space of cortex	Reduction in proportion to GFR (Eq. S6)	0.082		0.0098
$V_{PT,cell}$	L	Volume of water in proximal tubule cells		0.066		0.0079
$V_{PT,flt}$	L	Volume of proximal tubule filtrate		0.054		0.0064
$Q_{PT-U,flt}$	L/h	Filtrate flow rate out of proximal tubule		2.7		0.3
$CL_{PD,trans}$	L/h	Passive permeability by the transcellular routes		(Uptake) 0.89 (Bidirectional) 0.43		(Uptake) 0.11 (Bidirectional) 0.052
$CL_{PD,para}$	L/h	Passive permeability by the paracellular routes		(Uptake) 5.9 (Bidirectional) 2.9		(Uptake) 0.71 (Bidirectional) 0.34
$CL_{int,OAT2}$	L/h	CL_{int} of OAT2 transporter	INH scenario[d]: Reduction in proportion to GFR (Eq. S6). Non-INH scenario[d]: Additional deterioration in OAT2 (Eqs. S9,S10) + clearances of other transporters optimized (Eq. S11)	(Uptake) 20.8 (Bidirectional) 21.5	(Uptake) 2.49 (Bidirectional) 2.58	(Uptake) 1.40 (Bidirectional) 1.45
$CL_{int,OCT2}$	L/h	CL_{int} of OCT2 transporter		(Uptake) 23.9 (Bidirectional) 8.75	(Uptake) 2.87 (Bidirectional) 1.05	(Uptake) 5.47 (Bidirectional) 3.33
$CL_{int,MATE1}$	L/h	CL_{int} of MATE1 transporter		(Uptake) 0.16 (Bidirectional) 0.16	(Uptake) 0.019 (Bidirectional) 0.019	(Uptake) 0.036 (Bidirectional) 0.062
$CL_{int,MATE2-K}$	L/h	CL_{int} of MATE2-K transporter		(Uptake) 0.51 (Bidirectional) 0.53	(Uptake) 0.061 (Bidirectional) 0.063	(Uptake) 0.117 (Bidirectional) 0.200

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CL_{int}, intrinsic clearance; eGFR, estimated glomerular filtration rate; INH, intact nephron hypothesis; MATE, multidrug and toxin extrusion protein transporter; OAT2, organic anion transporter 2; OCT2, organic cation transporter 2.
[a]Values optimized for healthy patients, see Scotcher et al. (2019).[20]
[b]Assuming a man at age 65 years old with serum creatinine of 4.5 mg/dL, body weight of 70 kg, and height of 170 cm.
[c](Uptake); parameter values in uptake–OCT2 model, (Bidirectional); parameter values in bidirectional–OCT2 model.
[d]INH scenario – decline in transporter activity proportional to GFR, non-INH scenario – changes in transporter activity disproportionate to GFR (details in **Method** section).

average values for physiological model parameters for healthy subjects failed to capture increased $S_{Cr,baseline}$ in patients with CKD (gmfe = 2.33–2.34; **Figure S5**, **Table 2**). In particular, more pronounced underprediction of higher $S_{Cr,baseline}$ values was apparent. Refinement of the model to capture CKD-related decrease in glomerular filtration (**Eqs. S1,S2**) substantially reduced the gmfe with both creatinine models, but resulted in overestimation (gmfe = 1.37–1.38). Creatinine is produced in the muscle and R_{SYN} depends on WT, age, and sex.[22] R_{SYN} in the creatinine models for healthy subjects was based on young adult men,[29] whereas demographics of patients with CKD in this study were variable (e.g., WT range 44–96 kg). Consideration of both changes in GFR and R_{SYN} (**Eq. S5**) resolved the $S_{Cr,baseline}$ overprediction (gmfe = 1.14–1.15). However, certain underprediction was still evident, implying the necessity to consider additional factors contributing to decreased creatinine elimination in CKD.

Assuming INH decline in transporter activity, all transporter clearances were decreased 53% in G3 (GFR 59 mL/min/1.73 m^2) and 88% in G4 (GFR 15 mL/min/1.73 m^2; **Table 2**). This approach recovered observed $S_{Cr,baseline}$ (gmfe = 1.11–1.12; **Figure 3a,c**), but underestimation of C_{Cr}/GFR was evident (**Figure 3e,f**). Assuming decline in transporter activity disproportionate to GFR, deterioration of OAT2 activity was 65% or 93% in patients with GFR 59 and 15 mL/min/1.73 m^2, respectively (**Figure S4**). Estimated $Coeff_{CKD,TP}$ for uptake-OCT2 and bidirectional-OCT2 models were 0.88 and 0.70, respectively, resulting in less pronounced decrease in OCT2 and MATE-mediated clearances relative to GFR (e.g., when GFR decreases 88% (15 mL/min/1.73 m^2) relative to healthy, transporter clearances decrease 77% or 62% in uptake-OCT2 and bidirectional-OCT2 models, respectively). The non-INH scenario successfully recovered both $S_{Cr,baseline}$ (gmfe = 1.13; **Figure 3b,d**) and overall means of C_{Cr}/GFR in each CKD
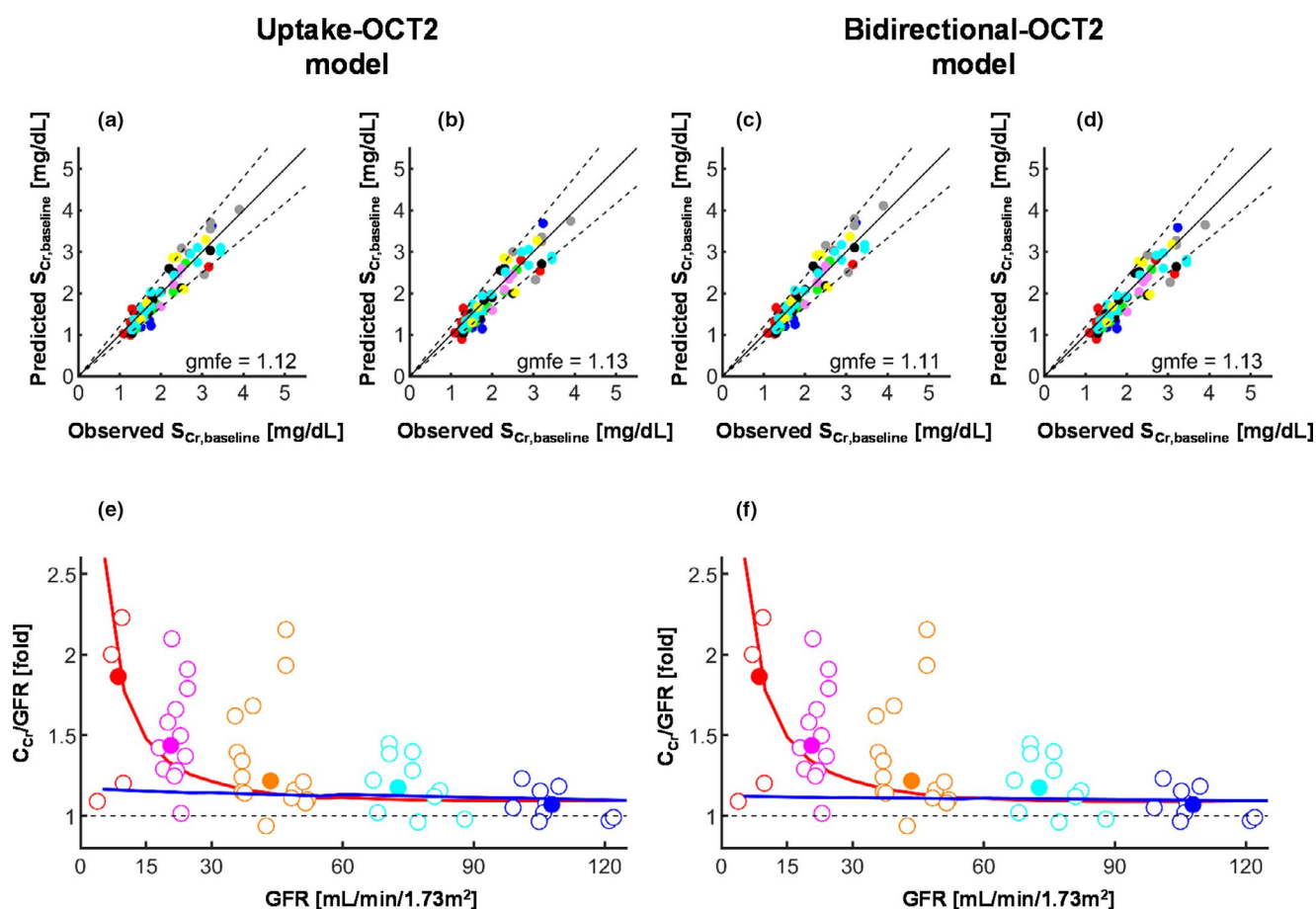

Figure 3 Development of creatinine chronic kidney disease (CKD) models. Predictability of serum creatinine ($S_{Cr,baseline}$, **a–d**) and ratios of creatinine clearance to glomerular filtration rate (GFR; C_{Cr}/GFR, **e** and **f**). Both creatinine uptake-organic cation transporter (OCT)2 model (**a**, **b**, **e**) and bidirectional-OCT2 model (**c**, **d**, and **f**) were optimized for patients with CKD based on two scenarios for transporter clearances: (**a**, **c**, and blue lines in **e** and **f**) decline in transporter activity proportional to GFR (intact nephron hypothesis (INH) scenario), (**b,d**, and red lines in **e** and **f**) changes in transporter activity disproportionate to GFR decline (non-INH scenario, details in Methods section). **a–d** Circles represent patients with CKD from 8 clinical studies (**Table 1**), and solid and dashed lines represent a line of unity and 1.2-fold error lines, respectively. gmfe, geometric mean fold-error. In figure **e** and **f**, open circles represent mean C_{Cr}/GFR in individual clinical studies and filled circles represent overall means for each CKD stage (**Figure S3**): blue = G1 (GFR > 90 mL/min/1.73 m^2), cyan = G2 (GFR 60–89mL/min/1.73 m^2), orange = G3 (GFR 30–59 mL/min/1.73 m^2), pink = G4 (GFR 15–29 mL/min/1.73 m^2), and red = G5 (GFR < 15mL/min/1.73 m^2). Blue and red solid lines are simulated C_{Cr}/GFR based on INH scenario and non-INH scenario for changes in transporter activity, respectively. Black dashed lines represent C_{Cr}/GFR = 1.

group (**Figure 3e,f**). Decrease in renal blood flow in CKD had marginal effect on $S_{Cr,baseline}$ (data not shown).

Verification of the developed creatinine CKD models was performed against independent datasets, including 42 patients with CKD (24 with G3 and 18 with G4, 22 men and 20 women, aged 22–68 years; **Table S8**); $S_{Cr,baseline}$ gmfe were < 1.32 for both INH and non-INH scenarios (**Figure S16**). Sensitivity analysis showed no sensitivity of $\%\Delta S_{Cr}$ to changes in GFR in INH scenario (i.e., models predicted comparable extent of interaction between heathy and CKD). In contrast, in the non-INH scenario, simulated $\%\Delta S_{Cr}$ in patients with CKD were higher relative to healthy patients in case of OCT2 or MATE inhibition, whereas the opposite trend was seen for OAT2 (**Figure S9**).

Pharmacokinetic models for renal transporter inhibitors in patients with CKD

A literature search identified one, four, and two clinical studies evaluating plasma concentration-time profiles of trimethoprim,[30] cimetidine,[31–33] and famotidine,[34,35] respectively, in patients with CKD (**Table 3**). Fraction of unbound inhibitors in plasma in patients with CKD was 0.51, 0.84, and 0.72 for trimethoprim, cimetidine, and famotidine, respectively (**Table S6**). These clinical data were used to develop operational PK models for each inhibitor (**Supplementary Material Section S6**).

Prediction of creatinine-drug interaction in patients with CKD

In total, 12 clinical studies (90 patients in CKD G3–4, age 22–88 years) were collated for the evaluation of the ability of creatinine CKD model to predict $\%\Delta S_{Cr}$ (**Table 1**). The effect of renal transporter inhibitors was initially simulated using unbound plasma concentration ($C_{p,u}$) as an inhibitory concentration against all transporters. Assuming that transporter activity changes disproportionately to disease-related changes in GFR resulted in higher predicted $\%\Delta S_{Cr}$ than the model with INH assumptions; this difference was more evident in the bidirectional-OCT2 model (**Figure 4**). Non-INH model assumptions resulted in 66% of predicted $\%\Delta S_{Cr}$ within prediction limits relative to 58% for the INH scenario; trends were consistent regardless of OCT2 directionality assumption (**Table S9**). Relatively higher predictability was seen for trimethoprim and famotidine (60 or 100% of studies within prediction limits, respectively), whereas underestimation of $\%\Delta S_{Cr}$ was seen for 40–60% of cimetidine studies regardless of the model. One potential contributor to this underprediction is the accumulation of inhibitors within the proximal tubule that was not accounted for when $C_{p,u}$ was applied as inhibitory concentration. Use of inhibitor concentrations in proximal tubular filtrate as a pragmatic/worst-case scenario for MATE transporters[21] improved overall predictability (75–83% within the prediction limits), except for the bidirectional-OCT2 model in the non-INH scenario (58% within the prediction limits; **Figure S17** and **Table S10**). Predictability of cimetidine interactions was overall improved regardless of the model (80–100% within the prediction limits).

In addition to prediction of the mean inhibitory effect per study, the predictability of individual $\%\Delta S_{Cr}$ was evaluated using the clinical data from 32 patients with CKD (G3; 18 patients, G4; 14 patients) that received trimethoprim (**Table 1**). The individual $\%\Delta S_{Cr}$ were highly variable (ranging from –20% to > 50%) in both CKD G3 and G4 (**Figure S18**). Simulations based on $C_{p,u}$ as an inhibitory concentration resulted in 34–47% of predicted individual data within assigned limits (**Table S11**). There was a tendency for higher prediction accuracy in CKD G3 (33–67% vs. 21–36% for patients with CKD G4), but this trend was based on a limited number of subjects.

DISCUSSION

Increased S_{Cr} post drug dosing requires careful interpretation because it can be caused by inhibition of renal transporters even in the absence of kidney injury, leading to the inappropriate discontinuation of medical treatments or misinformation in clinical trials in drug development.[2,36] Further consideration

Table 3 Pharmacokinetic studies of renal transporter inhibitors in patients with CKD

Inhibitor	Subject information (M; male, F; Female)	GFR, mL/min/1.73 m²	Study design	Blood sampling points, time after last dose	Reference
Trimethoprim	n = 9, M4 F5, 25–69 years	17–56	160 mg oral SD	1–48 hours	Rieder *et al.* (1974)[30a]
Cimetidine	n = 5, 26–76 years	30–52[b]	200 mg oral SD	0.75–9 hours	Larsson *et al.* (1979)[33c]
	n = 6, M4 F2, 43–66 years	23–47	Day 1–6; (200 mg × 4) per day oral Day7; 200 mg SD oral	0–9 hours on day 7	Larsson *et al.* (1981)[32d]
	n = 8, M6 F2, 31–68 years	36–69	Day1-6; (200 mg × 3 + 400 mg) per day oral Day7; 200 mg SD oral	0–9 hours on day 7	Larsson *et al.* (1981)[32e]
	n = 8, M8 F0, 34–66 years	23–65	300 mg intravenous SD	0.25–16 hours	Ma *et al.* (1978)[31f]
Famotidine	n = 5, M2 F3, 60–71 years	6–38[b]	20 mg oral SD	1–24 hours	Inotsume *et al.* (1989)[35]
	n = 12, M10 F2, 28–54 years	10–41	10 mg intravenous SD	2.5 minutes–4 hours	Abraham *et al.* (1987)[34]

CKD, chronic kidney disease; GFR, glomerular filtration rate; SD, single dosing.
[a] Subjects in G3-4 group (eGFR 15–59 mL/min/1.73 m²) was extracted based on individuals' eGFR
[b] Creatinine clearance (mL/min)
[c] Group with creatinine clearance of 30–52 mL/min
[d] Group with creatinine clearance of 30–50 mL/min
[e] Group with creatinine clearance of 50–75 mL/min
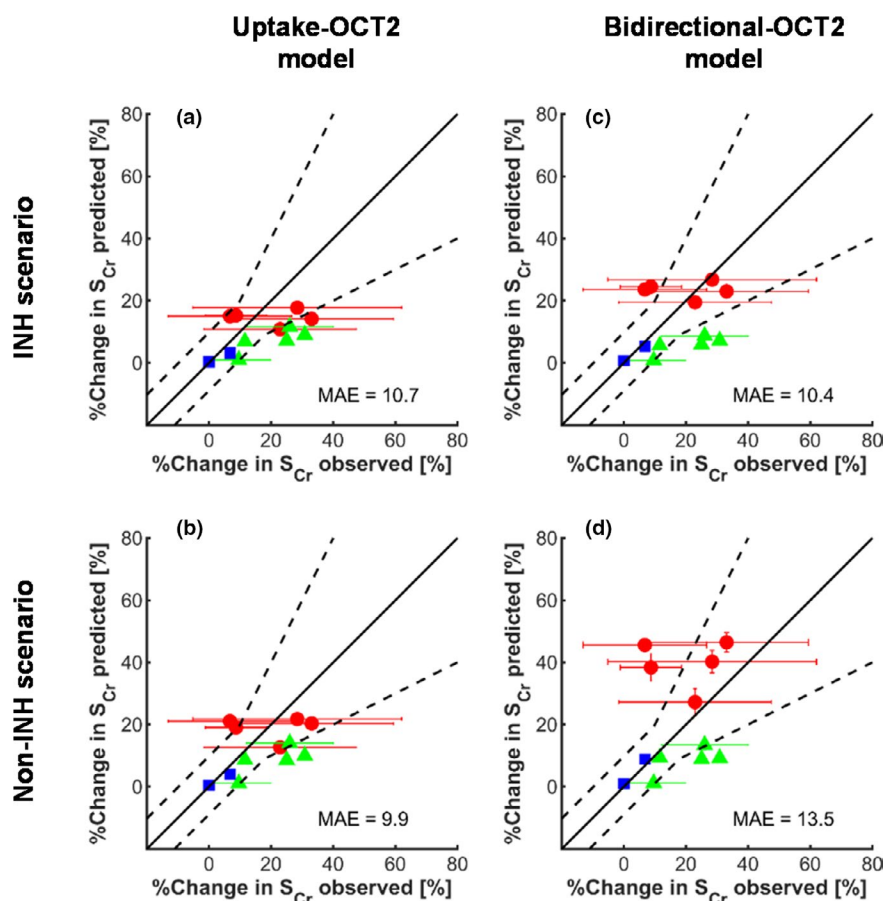[f] Group with creatinine clearance of 49–87 mL/min (mild renal failure).

Figure 4 Predictability of percent change in serum creatinine after administration of renal transporter inhibitors. Predicted percent change in serum creatinine (S_{Cr}) post administration of inhibitors using (**a,b**) uptake-organic cation transporter (OCT)2 model and (**c,d**) bidirectional-OCT2 model based on two scenarios for transporter clearances: **a,c** decline in transporter activity proportional to glomerular filtration rate (GFR; intact nephron hypothesis (INH) scenario), **b,d** changes in transporter activity disproportionate to GFR (non-INH scenario, details in Method section). Filled symbols and error bars represent means and standard deviations of percent change in S_{Cr} in each clinical study with three inhibitors; red circles = trimethoprim, green triangles = cimetidine, and blue squares = famotidine. Simulations were performed based on unbound concentrations of inhibitors in plasma as inhibitory concentration for all transporters. Solid and dashed lines represent line of unity and prediction error limits considering intra-individual variability in baseline S_{Cr} in the CKD population (8.9%), respectively. MAE, mean absolute error.

may be necessary for patients with CKD due to altered disposition of both creatinine and inhibitors as a result of the disease. Regulatory agencies have alerted about the possibility of altered drug-drug interactions in patients with impaired renal function.[37] Therefore, a tool elucidating the true cause of increased S_{Cr} in this patient cohort would be useful to improve decision making in clinical practice. Several studies have reported creatinine models that can simulate creatinine-drug interaction risk in healthy subjects,[18–21] but to the best of our knowledge, so far these efforts have not been extended to patients with CKD. This study showed a novel approach to simulate creatinine-drug interaction in patients with CKD using mechanistic physiologically-based pharmacokinetic models of creatinine combined with conventional PK models for inhibitors of renal transporters.

Patients with CKD in the Salford Kidney Study showed higher intra-individual variability in $S_{Cr,baseline}$ (8.9%) than healthy subjects (4.7%).[28] In addition, large interindividual variability in %ΔS_{Cr} was evident, consistent with previous clinical studies in the CKD population. The deterioration of renal function over

time (not considered in our model), could contribute to these variabilities in patients with CKD. A continuous increase in S_{Cr} due to the progression of CKD can result in a large change in S_{Cr} during the observation period, which could lead to the underestimation of true $S_{Cr,baseline}$ and potential overestimation of %ΔS_{Cr} (patient ID8 and 12; **Figure S1**). Higher interindividual variability in C_{Cr}/GFR in CKD (G3; 34% and G4; 42%) relative to healthy subjects (G1; 18%) may also contribute to large interindividual variability in %ΔS_{Cr} (**Table S5**).

Degree of creatinine-drug interaction in healthy subjects and patients with CKD

Only a few clinical studies compared the %ΔS_{Cr} with the same dosage regimen between healthy and CKD populations in a single clinical study.[38,39] Our comprehensive literature analysis showed the tendency for higher %ΔS_{Cr} in patients with CKD relative to healthy subjects at a daily dose of < 400 mg/day of trimethoprim (**Figure S2**). The overall comparison between two populations was based upon insufficient data to be conclusive on whether CKD leads to more pronounced

%ΔS$_{Cr}$. Nevertheless, higher interaction in the CKD population remains a possibility because dosage regimens of inhibitors had already been adjusted for reduced renal function in some studies reported in patients with CKD, possibly masking the difference between populations for trimethoprim (CKD = 33% vs. healthy = 15%) and famotidine (CKD = 7% vs. healthy = 1%),[38,39] albeit with larger variability in CKD.

Optimization of creatinine models for patients with CKD

In order to capture disease-related physiological changes, the creatinine CKD models included decreased glomerular filtration and modification of multiple physiological parameters based on several assumptions. For example, R_{SYN} regression equation accounted for differences in WT and age, based upon three independent clinical studies with subjects who did not show severe CKD (mean S$_{Cr}$ < 1.8 mg/dL)[40–42]; interindividual variability in R_{SYN} was < 35% regardless of age or sex (**Figure S6**). R_{SYN} was assumed to be unaffected by the progression of CKD because marginal changes in synthesis were reported in individuals with S$_{Cr}$ ranging from 1.5 to 5 mg/dL.[40] Application of INH assumptions to volumes of proximal tubule compartments, CL_{PD}, and $Q_{U\text{-filt}}$ was based on the principle that the number of proximal tubular cells, tubular surface area, and filtrate flow out of the proximal tubule are likely to decrease in proportion to the number of intact nephrons, respectively. Despite CKD-dependent changes occurring in filtrate pH and flow rate, fraction of creatinine reabsorbed in distal tubule was not affected, supported also by a previous study reporting no sensitivity of creatinine renal clearance to these parameters.[9]

In addition to INH assumptions, where transporter activity declines proportionally to GFR, an alternative scenario was explored in the creatinine CKD model, assuming changes in transporter clearances that are not consistent with the GFR decline. Deterioration of OAT2 activity implemented in this non-INH scenario (65–93%) was comparable to those reported for OAT1/3 (66–95%).[6] In the case of OCT2 and MATEs, relative decline in transporter activity was smaller compared with proportional changes assumed under the INH. Further investigations are necessary to elucidate fully changes in the functional activity of OCT2 and MATEs in patients with CKD.

Predictability of creatinine CKD models

Following non-INH assumptions for transporter clearances, creatinine CKD models showed higher sensitivity to inhibition of OCT2/MATEs relative to models for healthy populations; opposite trend was seen for OAT2 (**Figure S9**). These differences are attributed to changes in fraction transported and change in overall contribution of secretion compared with filtration and reabsorption in the non-INH scenario. In contrast, CKD models assuming decline in transporter activity proportional to GFR (INH scenario) showed similar sensitivity to transporter inhibition to healthy subjects, because fraction of creatinine transported by renal transporters were minimally affected under these assumptions.

Higher sensitivity of the models with non-INH transporter assumptions to creatinine-drug interactions was also reflected in the predictive performance of %ΔS$_{Cr}$ (**Figure 4**). Simulations of the %ΔS$_{Cr}$ based on $C_{p,u}$ as inhibitory concentration for all transporters resulted in 66% of clinical studies within the proposed prediction limits (**Table S9**) and improved predictive performance to healthy population (59% and 51% in uptake-OCT2 and bidirectional-OCT2 model, respectively).[21] Underestimation of %ΔS$_{Cr}$ for cimetidine and improved predictability with $C_{PT,filt}$ were consistent between creatinine models for CKD and healthy populations.[21] Use of $C_{PT,filt}$ tended to exacerbate overestimation of trimethoprim-creatinine interactions in CKD. The original creatinine models[20,21] were optimized with trimethoprim interaction in healthy subjects and with $C_{p,u}$ as inhibitory concentration for all transporters. This approach may have resulted in bias by compensating for the difference in the inhibitor concentration in plasma and the proximal tubular filtrate, leading to the overestimation of trimethoprim interaction when $C_{PT,filt}$ was applied. The application of $C_{PT,filt}$ was a pragmatic approach to explore the worst-case scenario. Improved predictability for cimetidine and overestimation for trimethoprim with $C_{PT,filt}$ highlight potential limitations of empirical PK models ignoring the intracellular concentration of inhibitors in proximal tubular cells. Mechanistic modelling of inhibitors,[43,44] which was beyond the scope of current work, would enable us to address these limitations.

Despite reasonable recovery of the mean observed %ΔS$_{Cr}$ per study, interindividual variability of %ΔS$_{Cr}$ was not captured by the proposed creatinine CKD models. Multiple factors could contribute to the underestimation of the extent of this interindividual variability. Empirical compartment PK models of inhibitors could not consider interindividual variability in the inhibitors' plasma exposure due to limited data. PK data from patients with CKD G3 and G4 were not differentiated in the development of these PK models, potentially resulting in underestimation of the impact of CKD severity on the PK of these drugs. In addition, lack of description of disease progression and longitudinal changes in GFR and other physiological parameters or interindividual variability in C$_{Cr}$/GFR in the model may contribute to underestimation of interindividual variability in %ΔS$_{Cr}$.

In conclusion, elevation of S$_{Cr}$ is likely to be interpreted as acute kidney injury and can result in the discontinuation of new drug development or clinical treatment. Inhibition of renal transporters also causes elevated S$_{Cr}$, as observed in our creatinine-trimethoprim interaction study in patients with moderate-to-severe CKD. The developed creatinine CKD model enabled quantitative prediction of the increase in S$_{Cr}$ resulting from deteriorated renal function and identified challenges in quantitative translation to patients. In addition, modelling allowed differentiation of the effect of disease from inhibition of renal transporters with the ultimate goal to provide a valuable tool for prospective evaluation of drug interaction risk via renal transporters in this patient population.

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