Chapter 4
Pharmacometrics in Chronic Kidney Disease

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4.1 Introduction

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting both structure and function of the kidney. Coupled with aging population and higher prevalence of diabetes mellitus and hypertension, CKD has become a leading public health concern worldwide. National Health and Nutrition Examination Survey suggested the prevalence is 38 % in elderly (age ≥ 65 years) and 13 % in the overall US population (Coresh et al. 2007). A similar inexorable increase in the number of patients receiving chronic renal replacement therapy (RRT) by dialysis or transplant is seen in the past decade (Kidney Disease Statistics for the United States [Internet] 2013). CKD is a common and deadly disease (Levey et al. 2007).

The kidney performs endocrine functions (erythropoietin, renin, calcitriol), metabolizes small peptide hormones, produces glucose via gluconeogenesis, maintains homeostasis (solutes, water), and eliminates endogenously produced "waste products" (uremic toxins). Pathophysiologic changes associated with CKD affect other organ systems in the body and have pronounced effects on the pharmacology of many drugs. Rational drug therapy in subjects with CKD must take into account changes in the absorption, distribution, metabolism, and excretion (ADME) of drugs and their active or toxic metabolites due to impaired kidney. To complicate the matter further, a majority of subjects with CKD receive multiple drugs for the treatment of underlying diseases such as hypertension, diabetes mellitus, infection-

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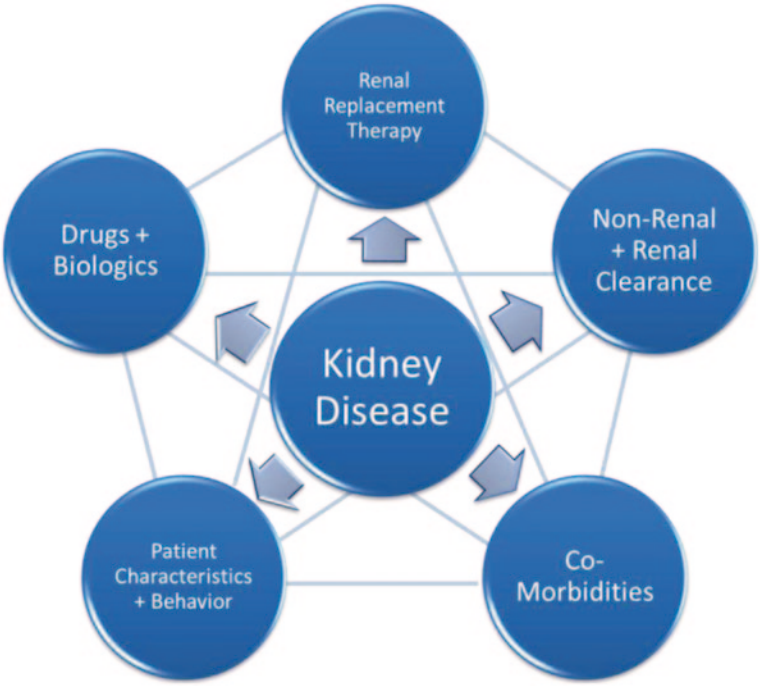

Fig. 4.1 Complex interplay between therapies and CKD

related or autoimmune diseases (e.g., systemic lupus erythematosus). Some of these treatments have renoprotective effects; others are associated with nephrotoxic effects.

The learning for clinical efficacy/safety balance of emerging medicines is vastly based on a general population. Quantitatively extrapolating the knowledge and individualizing such balance for subjects with CKD are not straightforward. Why? The interactions between CKD and treatment are not just unidirectional. Multifaceted factors need to be considered when medicines for subjects with CKD are developed and utilized: (1) altered renal and *non*-renal clearance can affect drug exposure and effects in CKD, (2) drugs for comorbidities or underlying diseases can have nephrotoxic effects and accelerate progression of CKD, (3) progression of CKD requires careful monitoring and frequent adjustments of treatments, (4) RRT by dialysis or transplant can impact drug exposure and effects, and (5) RRT can change a patient's behavior (e.g., drug non-adherence), which in turn can affect drug exposure and clinical outcomes (Fig. 4.1).

This complex interplay between CKD-related multifaceted factors that interact with therapeutics calls for quantitative approaches to optimize therapies for subjects with CKD. Pharmacometrics is a quantitative scientific discipline that uses mathematical models based on biology, pharmacology, physiology, and knowledge in disease for quantifying interactions between disease, drugs, and patients (Zhang et al.

Table 4.1 Five stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

2008; Pfister and D'Argenio 2010). Pharmacometric approaches have been increasingly applied to understand and characterize interactions between CKD-related factors and therapeutics in the recent years (Pfister et al. 2012).

The goal of this book chapter is to review and discuss opportunities for applying pharmacometrics for facilitating research and development of new drugs in CKD, optimizing development and utilization of medicines in CKD and managing RRT such as dialysis and kidney transplant. A background on CKD and the interactions between CKD, RRT, and therapeutics is given before the introduction of case studies for the application of pharmacometrics in these areas.

4.2 Background on CKD

This section provides an overview of stages, risk factors, and consequences of CKD, assessment of kidney function, effects of CKD on drugs, effects of drugs on CKD, and interactions between drugs and RRT by dialysis or transplant.

4.2.1 Define CKD and its Five Stages

All individuals with kidney damage or a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for 3 months are classified as having CKD. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Five stages of CKD are classified based on the presence of kidney damage or GFR level (Table 4.1; KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification [Internet] 2013).

4.2.2 Risk Factors and Consequences of CKD

CKD is a silent disease. It is critical to screen for CKD and its risk factors to detect any kidney damage early (Fig. 4.2). Cardiovascular risk factors, such as old age, hypertension, dyslipidemia, smoking, and diabetes mellitus promote the development

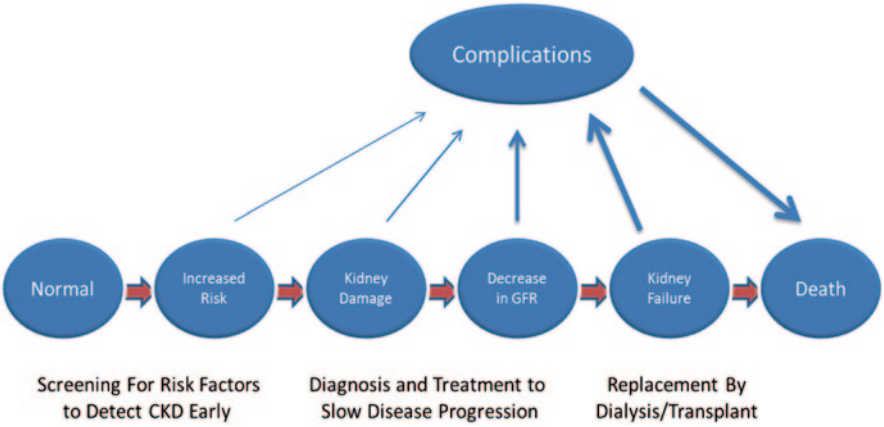

Fig. 4.2 CKD: a silent deadly disease. *GFR* glomerular filtration rate

and progression of both CKD. A direct relationship was observed between the prevalence of CKD and markers of insulin resistance, such as levels of serum insulin, C-peptide, and glycosylated hemoglobin A1c. Family history, low birth weight, race (African Americans), and gender (male) are also shown to be risk factors for CKD. Meanwhile, patients in all stages of CKD are considered at risk for development of cardiovascular disease and CKD is recognized as a cardiovascular risk equivalent. Not only uremic toxins but also homocysteine, lipoproteins, and markers of inflammation and oxidative stress are elevated in CKD.

4.2.3 Assess and Monitor Kidney Function

Filtration markers such as inulin, iohexol, and iothalamate are considered the gold standards for measuring GFR. However, GFR is more commonly estimated using equations for practicality reason. The Cockroft–Gault (C–G) equation was developed in 1976 to estimate urinary creatinine clearance (in units of ml/min) with data from 249 Caucasian men with a mean creatinine clearance of 73 ml/min (Cockcroft and Gault 1976):

$$\mathrm{GFR(ml/min)} = (140 - \mathrm{age}) \times \mathrm{weight}/(72 \times \mathrm{Scr}) \times (0.85 \text{ for female subjects})$$

In 1999, the modification of diet in renal disease (MDRD) study equation was developed to estimate GFR measured with data from 1628 men and women, including African Americans and Caucasians with a mean GFR of 40 ml/min/1.73 m^2 (Levey et al. 1999).

$$\mathrm{GFR(ml/min/1.73\ m^2)} = 186 \times \mathrm{Scr} - 1.154 \times \mathrm{age} - 0.203 \times (0.742 \text{ for female subjects}) \times (1.212 \text{ for African Americans})$$

Comparing with C–G equation, which is a measure of kidney filtration on an absolute scale, the MDRD study equation is normalized to body surface area (BSA) of 1.73 m^2 and is more suitable to judge renal impairment because it adjusts for the expected normal increase in absolute filtration with body size. However, the MDRD study equation underestimates measured GFR at levels > 60 mL/min/1.73 m^2, with variable accuracy among subgroups (Stevens et al. 2010). For this reason, a new GFR-estimating equation, the CKD epidemiology collaboration (CKD-EPI) equation, was developed (Levey et al. 2009). The CKD-EPI equation was found to be more accurate than the MDRD study equation overall and across most subgroups. The CKD-EPI creatinine equation is based on the same four variables as the MDRD study equation, but uses a 2-slope "spline" to model the relationship between estimated GFR (eGFR) and serum creatinine, and a different relationship for age, sex, and race. The CKD-EPI creatinine equation was reported to be more accurate than the MDRD study equation across a wide variety of populations and clinical conditions (Levey et al. 2009; Levey and Stevens 2010; Stevens et al. 2011).

In the future, other GFR estimating equations may be developed that outperform CKD-EPI. The CKD-EPI creatinine equation is:

$$\mathrm{GFR} = 141 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}}$$
$$\times 1.018 \text{ if female} \times 1.159 \text{ if black}$$
$$\kappa = 0.7 \text{ if female}$$
$$\kappa = 0.9 \text{ if male}$$
$$\alpha = -0.329 \text{ if female}$$
$$\alpha = -0.411 \text{ if male}$$
$$\min = \text{The minimum of Scr}/\kappa \text{or } 1$$
$$\max = \text{The maximum or Scr}/\kappa \text{or } 1$$

A recent meta-analysis of data from 1.1 million adults (aged≥18 years) indicated that the new CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and end-stage renal disease (ESRD) than did the MDRD study equation across a broad range of populations (Matsushita et al. 2012).

Recently, new biomarkers were evaluated to detect and monitor kidney injury/disease, including cystatin C for drug-induced kidney toxicity, urinary β2-microglobulin for earlier and more sensitive measure of kidney tubular toxicity, and kidney injury molecule-1 for detecting early kidney injury in adults and pediatrics (Parikh et al. 2011; Mårtensson et al. 2012). These new biomarkers were additional to the routinely used biomarkers including levels of serum creatinine, BUN, and urinary N-acetyl-glucosamine, glycosuria, and proteinuria. Research, development, and use of new drugs for therapeutic targets associated with diseases associated with deterioration in kidney function, such as diabetes mellitus, hypertension, obesity, heart failure, hyperlipidemia, and transplant rejection may benefit from measuring and modeling such biomarkers.

4.2.4 Understand Impact of CKD on Exposure and Effects of Drugs and Biologics

A progressive decline in kidney function, a hallmark of CKD, often leads to a wide array of the pathophysiologic changes that affect the absorption, distribution, metabolism, and excretion (ADME) characteristics of drugs (Table 4.2), including decreased glomerular filtration and/or renal transport, altered absorption, bioavailability, and/or protein binding (Naud et al. 2012; Joy 2012).

Evidence is also emerging on the impact of CKD on the non-renal clearance of many drugs, specifically affecting uptake and efflux transporters as well as metabolic enzymes in the liver and gastrointestinal tract (Nolin and Unruh 2010). Recent studies suggest that accumulated uremic toxins in subjects with CKD can cause either transcriptional or translational modifications or direct inhibition of these enzymes (e.g., CYP2C11, CYP3A1, CYP3A2) and transporters (e.g., organic anion transporting peptide, OATP; Nolin et al. 2008; Dreisbach 2009). Such pathophysiological changes can explain altered exposure and response of renally and some non-renally eliminated drugs in subjects with CKD.

Protein therapeutics (biologics) are eliminated from the body nearly exclusively by proteolysis. Theoretical considerations and clinical evidence suggest that the kidneys play a relevant role in the catabolism and thus elimination of biologics that have a size below the cutoff for glomerular filtration of approximately 60 kDa. Thus, the effect of CKD on biologics seems to be predictable and only relevant for compounds below this molecular weight cutoff. This is supported by clinical evidence that shows a lack of effect of kidney function on large proteins such as monoclonal antibodies, whereas smaller proteins below the cutoff such as interleukin-10, growth hormone and erythropoietin experience a gradual decrease of their clearance and increase of their systemic exposure with increasing degree of impaired kidney function (Kim et al. 1995; Meibohm and Zhou 2012).

4.2.5 Understand Effects of Drugs on CKD

Much of the differences between drug responses in CKD patients and regular population can be explained by the exposure difference between the two. Altered ADME property of drugs in subjects with CKD leads to different exposure in active drug or metabolites (Table 4.2), which in turn causes difference in responses. Perhaps for this reason, in the *Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling* issued by Food and Drug Administration (FDA; Tortorici et al. 2012; Draft Guidance: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet] 2010), the guidance listed detailed instruction for pharmacokinetic (PK) testing but only vaguely mentioned pharmacodynamic (PD) assessment should be included in the testing when appropriate. Dose for subjects with CKD are typically adjusted to produce a comparable range of unbound plasma concentrations of drug of active metabolites in the patients with normal kidney function.

Table 4.2 Impact of CKD on absorption, distribution, metabolism, and excretion (ADME) of drugs

	CKD-related pathophysiological changes	Effect on drugs	Impact
Absorption	Formation of ammonia in the presence of gastric urease and buffers gastric acid	Decreased absorption of drugs that are best absorbed in an acidic environment, prolongs gastric emptying, and delays drug absorption	More variable bioavailability in patients with renal impairment than in patients with normal renal function
	Increase in gastric pH	Increased amounts of active drugs in the systemic circulation and enhanced bioavailability of some drugs	
	Decrease in first-pass hepatic metabolism and biotransformation	More unbounded drugs to be available at the site of hepatic metabolism, thereby increasing the amount of drug removed during the hepatic first pass	
	Decrease in protein binding		
Distribution	Formation of edema and ascites	Increased apparent volume of distribution of highly water soluble or protein bound	Lower plasma concentrations after a given dose
	Decrease in albumin concentration	Decreased affinity for the drug reduces protein binding in patients with uremia, making the unbound fraction of acidic drugs substantially increased	More abundant drug available at the site of drug action or toxicity
	Removal of fluid during dialysis	Altered distribution volume of drugs and change during the dialysis cycle	Different concentration within dialysis cycle
Metabolism	Accumulation of uremic toxins	The rate of reduction and hydrolysis reactions and microsomal oxidation are reduced	Accumulated active drug
		Glucuronidation to polar, water-soluble metabolites is impaired due to decreased clearance of blucuronide from plasma	Slows down the removal of soluble metabolite
		Alternations of intestinal, hepatic, and renal transporters, and metabolic enzymes such as reduced OATP expression and altered CYP expression	Higher incidence of adverse drug reactions
		May also alter the disposition of drugs metabolized by the liver through changes in plasma protein binding while the unbound intrinsic metabolic clearance declines with creatinine clearance	

Table 4.2 (continued)

	CKD-related pathophysiological changes	Effect on drugs	Impact
Excretion	Decrease in GFR	Clearance of drugs eliminated primarily by glomerular filtration	Increased plasma concentration and prolonged half-life in drug that are eliminated primarily by glomerular filtration
	Decrease in protein binding	Decreased filtration of drugs; may also increase the amount secreted by the renal tubule	The excretion of drugs eliminated by active organic ion transport systems in the renal tubules is prolonged in patients with CKD and may become saturated upon multiple drug administration
	Decrease in enzymatic capacity	Decreased metabolism, including many protein and small peptides	Increased concentration and prolonged half life

In epidemiology studies, CKD has been shown to be a risk factor for cardiovascular diseases, hematologic diseases, endocrine diseases, neurologic disease, and may lead to mineral bone disorders (MBDs; Briasoulis and Bakris 2013; Levin 2013). It is foreseeable that the efficacy and safety of these diseases could be different in subjects with CKD and subjects with a different degree of CKD. For drugs that rely on kidney function to exert its effect, the responses in subjects with CKD are expected to be different. Sodium-glucose cotransproter-2 (SGLT2) inhibitors developed for the treatment of type 2 diabetes mellitus (T2DM) by decreasing glucose reabsorption in kidney are shown to rely on a close-to-normal kidney function to exert its full pharmacological effect on glucose (Komoroski et al. 2009; Kasichayanula et al. 2012).

The kidneys are vulnerable to injury due to their high filtration capacity and high metabolic activity, and most drugs, especially hydrophilic drugs and their metabolites, are eliminated largely by kidneys in urine, thus increasing the risk of drug-induced nephrotoxicity (DIN). DIN accounts for approximately 20 % of community- and hospital-acquired episodes of acute kidney injury (AKI), and AKI is a risk factor for the future development or accelerated progression of CKD (Goldstein et al. 2013).

Manifestations of DIN include acid–base abnormalities, electrolyte imbalances, urine sediment abnormalities, proteinuria, pyuria, hematuria, and decrease in GFR. Aminoglycoside antibiotics, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and radio-contrast media have been frequently associated with DIN, especially in patients with CKD. Anti-hypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor inhibitors (ARBs)

have renoprotective effects by lowering both blood pressure and proteinuria and are the preferred treatment option in CKD with T2DM. At the same time, the use of ACE inhibitors and ARBs can result in adverse effects, which are more common in CKD. The most common side effects-early decrease in GFR, hypotension, and hyperkalemia-require careful monitoring of therapy, but can usually be managed without discontinuation of the agent.

In a recent study in subjects with T2DM and CKD, bardoxolone methyl, an oral antioxidant inflammation modulator, was not lowering proteinuria, but was associated with an increase in eGFR (Pergola et al. 2011).

4.2.6 Understand Effects of Drugs on Kidney Transplants

In transplant medicine, the standard immunosuppressive treatment paradigm for prophylaxis of organ rejection in kidney transplant can be classified into the following three stages (Halloran 2004): (1) induction of immunosuppression (usually with immune-cell-depleting agents), (2) pre-adaptive maintenance therapy (with a combination of a calcinurin inhibitor (CNI; cyclosporin or tacrolimus), an antimetabolite (azothioprene) or nucleotide synthesis inhibitor (mycophenolatemofetil, MMF), and a glucocorticoid), and (3) post-adaptive maintenance therapy with lower dose of the three pre-adaptive therapy drugs. Ironically, CNIs such as cyclosporine are associated with nephrotoxic effects: Acute nephrotoxicity caused by vascular dysfunction and a more chronic fibrotic form. CNIs therefore require therapeutic drug monitoring due to their narrow therapeutic window (Schiff et al. 2007). As noted above, CNIs are often given in combination with MMF, the dose of which is also adjusted based on therapeutic drug monitoring (Kuypers et al. 2010). To complicate matters further, CNIs exhibit time-dependent PK, are eliminated primarily by CYP3A4, and are therefore prone to interactions with other drugs that affect the activity of this enzyme (Lukas et al. 2005; Park et al. 2007), and mycophenolic acid (MPA, the active moiety of MMF) undergoes enterohepatic recycling, the biliary excretion of which is inhibited by cyclosporine A (CsA) (Hesselink et al. 2005). The area under curve (AUC) of MPA for a given dose of MMF can vary by tenfold, and increasingly sophisticated PK models describing the enterohepatic recycling of MPA have been proposed to explain the source of this variability (Sherwin et al. 2011), to enable more precise dose adjustment for this narrow therapeutic window drug.

4.3 Applications of Pharmacometrics in CKD

CKD presents a wide array of treatment-related challenges that are associated with high costs and poor outcomes. Pharmacometric approaches have been frequently applied to understand the interactions between CKD and therapeutics spanning from basic research into disease and mechanisms of drug action to the rational use of medicines in patient care. Innovative and strategic application of quantitative

methods in conjunction with well-designed trials for characterizing drug exposure, efficacy, and toxicity, will benefit patients with CKD. Pharmacometrics provides the foundation for this multidisciplinary effort that involves basic and applied university researchers, industry drug development scientists and decision makers, government regulatory scientists, clinicians, and other health professionals. An appreciation and understanding of opportunities for pharmacometrics in CKD (Table 4.3) call for a sustained collaborative effort between all stakeholders involved in developing and utilizing therapeutics for CKD and related comorbidities.

4.3.1 Quantify the Impact of CKD on Exposure and Effects of Drugs

Pharmacometric approaches are widely used to characterize the impact of CKD on exposure and effects of drugs and biologics. Both mechanism-based and empirical models are developed and applied, given modeling objectives. In the mechanistic models, the function formats of the models are elucidated by the understanding of underlying drug, disease, and CKD physiologic mechanisms. The models include knowledge, data, and scientific perspective from many relevant aspects and are constantly updated. Predictability is the key model performance requirement. In the empirical models, the influence of CKD on drug exposure and effects are typically expressed by including renal function as a covariate on the parameter(s) of the conventional exposure and response models. Treating renal function as a continuous variable, such as using eGFR values in the analysis, is usually preferred to an analysis which treats it as a categorical variable per degree of CKD.

A recently published physiologically based, multi-scale model of calcium homeostasis and bone remodeling describes the impact of progressive loss of kidney function over a typical 10-year course of CKD, including the evolution of secondary hyperparathyroidism, a sequel of which is Mineral Bone Disorder (MBD) (Riggs et al. 2012). This multi-scale physiologic model described CKD-MBD-related clinical changes in phosphate, parathyroid hormone, and calcitriol and linked bone remodeling markers with bone mineral density (BMD) elimination and formation rates. The composite multi-scale model was able to predict lumbar spine BMD losses up to 10 years in various renal function groups (Fig. 4.3) and simulate interventions with a hypothetical calcimimetic agent and calcitriol. This multi-scale mechanism-based model is a quantitative summary on the changes in CKD-MBD from signal to organs and to clinical outcomes. It provided a platform for projecting the CKD disease response and for evaluating therapeutics.

Zhang et al. (2010) provided another example of mechanistic model in CKD, which characterized the exposure and response of the SGLT2 inhibitor, a therapeutic agent developed for the treatment of T2DM. SGLT2 inhibition leads to decreased glucose reabsorption which in turn results in glucose excretion in theurine. This is expected to lower plasma glucose concentrations and urinary loss of excess calories at the same time. The relationship between plasma glucose concentration,

Table 4.3 Opportunities for pharmacometrics in CKD

Opportunities		Approaches
Understand interactions between CKD and Therapeutics	Describe progression of CKD and characterize its effect on other organs	Develop mechanism-based disease models (e.g., model that describes effects of CKD on bone mineralization)
	Facilitate design, conduct, and interpretation of trials in subjects with CKD	Stage kidney function by eGFR (rather than by creatinine clearance)
		Complement trials with integrated pharmacometric analyses
	Investigate impact of drugs on CKD outcomes	Apply model-based meta-analysis to investigate relationships between drugs and CKD outcomes
	Characterize impact of impaired CKD on drugs	Understand impact of CKD on non-renal drug clearance
		Integrate exposure, efficacy, and safety data from phase 1, 2, and/or 3 studies to characterize efficacy/safety in patients with impaired kidney function
		Quantify and understand exposure-efficacy/safety balance (i.e., therapeutic utility) in subjects with CKD
Understand interactions between RRT and Therapeutics	Quantify impact of RRT on drugs	Consider factors that impact removal of drugs in adult and pediatric patients receiving HD
		Apply model-based trial simulation (i.e., pharmacometric approaches) to guide use of drugs in patients receiving HD
	Fine-tune RRT in adults and pediatrics	Explore alternative HD schedules, such as daily short HD or long nocturnal HD
		Define new metrics for assessing and fine-tuning conventional and newer HD modalities
Understand interactions between Kidney Transplant and Therapeutics	Characterize drug effects in kidney transplantation	Utilize pharmacometric approaches to characterize time-dependent drug exposure and effects
	Explore drug non-adherence on kidney transplantation outcomes	Explore patient characteristics (e.g., underlying disease, comorbidities, co-medications) and behavior such as drug adherence

Table 4.3 (continued)

Opportunities		Approaches
Optimize use of Therapeutics in subjects with CKD	Evaluate and optimize dose adjustments in subjects with CKD	Determine relationships between drug exposure and kidney function in order to report renal dosing adjustment recommendations
	Enhance labels for subjects with CKD	Apply pharmacometric approaches to identify safe and efficacious dosing in subjects with CKD

renal glucose excretion threshold, and the amount of glucose in urine can be directly measured in a small number of patients through a well-designed hyperglycemic clamp study (Polidori et al. 2013); however, a modeling approach provided a way to use more data collected in clinical development, sample across a much larger and more heterogeneous population, and link the mechanism-specific biomarkers to long-term disease end points. The model encompassed the factors that could disturb

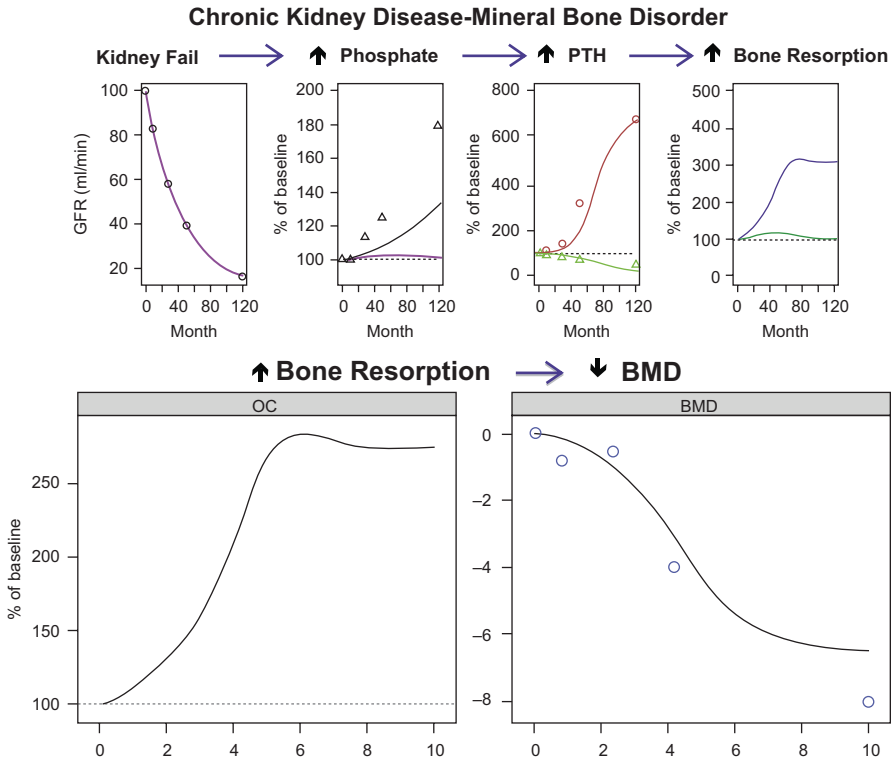

Fig. 4.3 Multi-scale physiology-based modeling of MBD in CKD. *BMD* bone mineral density *PTH* Parathyroidhomone, *MBD* Mineral Bone Disorder

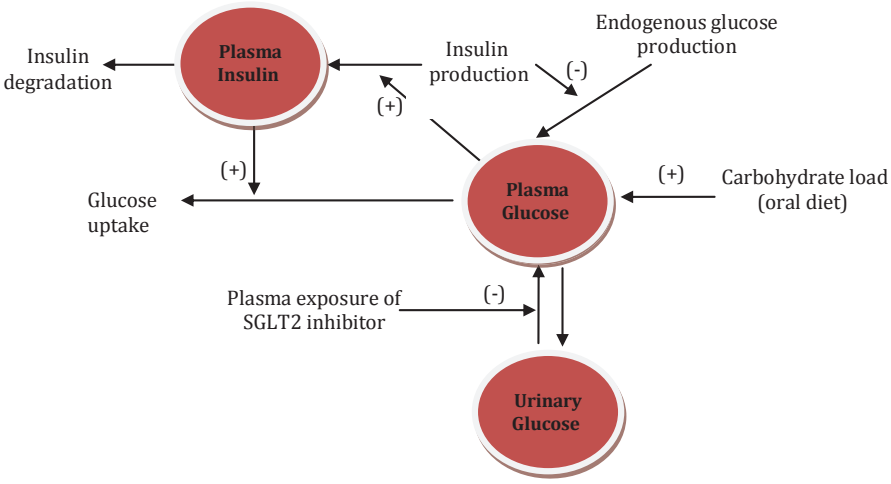

Fig. 4.4 Modeling urinary glucose excretion upon SGLT2 inhibition

the homeostasis of glucose metabolism, including endogenous glucose production, carbohydrate load, and plasma exposure to an SGLT2 inhibitor and predicted glucose amount in urine and glucose concentration and insulin concentration in urine (Fig. 4.4). The projected exposure of SGLT2 inhibitor and the response of glucose excretion at various levels of GFR can also be predicted.

The SGLT2 inhibitor dapagliflozin is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A9 to dapagliflozin 3-O-glucuronide. As UGT1A9 is expressed in the kidney and the liver, both impaired hepatic and kidney function may impact the metabolic clearance of dapagliflozin. A semi-mechanistic model was developed for dapagliflozin and its inactive metabolite dapagliflozin 3-O-glucuronide (D3OG) with emphasis on renal and hepatic contribution to dapagliflozin metabolism (van der Walt et al. 2013). Impaired hepatic and kidney function decreased the clearance of dapagliflozin to D3OG and the clearance of D3OG. The fraction of D3OG formed via the renal route decreased from 40 to 55% in subjects with normal kidney function (creatinine clearance CrCL > 80 mL/min) to 10% in subjects with severely impaired kidney function (CrCL = 13 mL/min). Model-based simulations suggested that the increase of systemic exposure (AUCss) of dapagliflozin and D3OG was less than twofold in subjects with mild or moderate impairment of kidney function. This semi-mechanistic model presents a useful approach to evaluate the impact of kidney *and* hepatic function on the PK of dapagliflozin (Fig. 4.5).

Semi-mechanistic models were also applied to quantify non-renally eliminated drugs such as sildenafil, repaglinide, and telithromycin in subjects with CKD (Zhao et al. 2012) or to generate insight into the likely mechanism (inter-conversion) of the increased exposure of tesaglitazar in subjects with CKD (Hamrén et al. 2008).

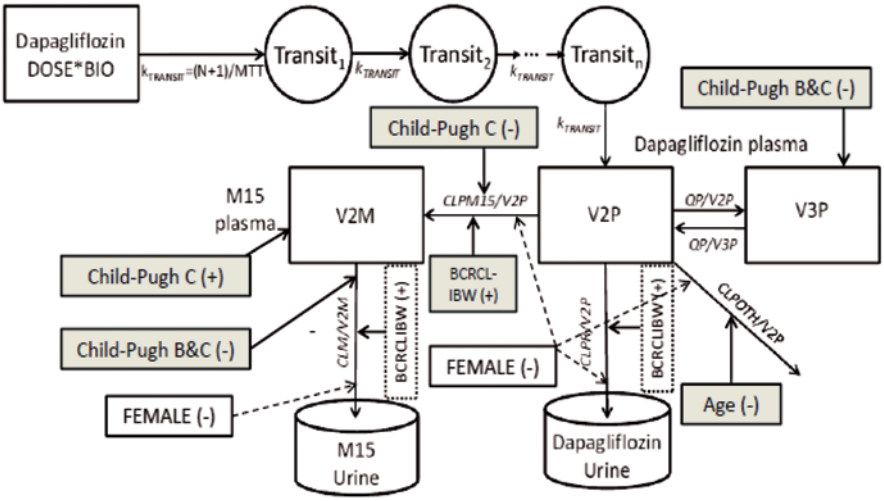

Fig. 4.5 Modeling renal and non-renal elimination of dapagliflozin and D3OG in T2DM subjects with impaired kidney and/or hepatic function (van der Walt et al. 2013). Covariates connected to compartments affect the relevant volume, those connected to pathways affect the relevant clearance. *BCRCLIBW* baseline creatinine clearance calculated using ideal body weight (IBW), *CLM* renal clearance of D3OG, *BIO* bioavailability, CLP_{M15} metabolic clearance of dapagliflozin to D3OG, CLP_{other} metabolic clearance of dapagliflozin to unmeasured metabolites, CLP_{renal} renal clearance of unchanged dapagliflozin to urine, *MTT* mean transit time, *N* number of transit compartments, *QP* inter-compartmental clearance of dapagliflozin, T2DM type 2 diabetes mellitus, *V2P* central volume of distribution of dapagliflozin, *V3P* peripheral volume of distribution of dapagliflozin, *V2M* central volume of distribution of D3OG. *Dashed lines* a priori scaling, *shaded areas* covariates selected during step-wise covariate model building, *unshaded areas* added based on previous modeling experience

4.3.2 Quantify the Impact of Dialysis on Drug Exposure

Treatments for stage V of CKD encompass four types of life-supporting RRT: hemodialysis (HD), peritoneal dialysis, hemofiltration, and kidney transplantation. HD is the most common RRT option. Quantifying the impact of HD on drugs is often a regulatory requirement as well as a clinical practice necessary for optimizing dosing regimen and dialysis prescription. The increased use of more intensive, nonstandard HD regimens other than the conventional three times a week for 3- to 4-h treatments presents additional need for quantification of the impact of dialysis on Drug exposure.

A pharmacometric approach was applied to quantify the impact of CKD and HD on the removal of saxagliptin and its active metabolite 5-hydroxy saxagliptin (Zhang et al. 2012a). Exposures of saxagliptin and its active metabolite 5-hydroxy saxagliptin were predicted at different dose levels during and between HD sessions (Fig. 4.6). A similar approach was used to quantify the dialysis impact on entecavir (Bifano et al. 2010) and candesartan (Pfister et al. 1999). The entecavir work was directly related to the approved label of entecavir for use in subjects with CKD,

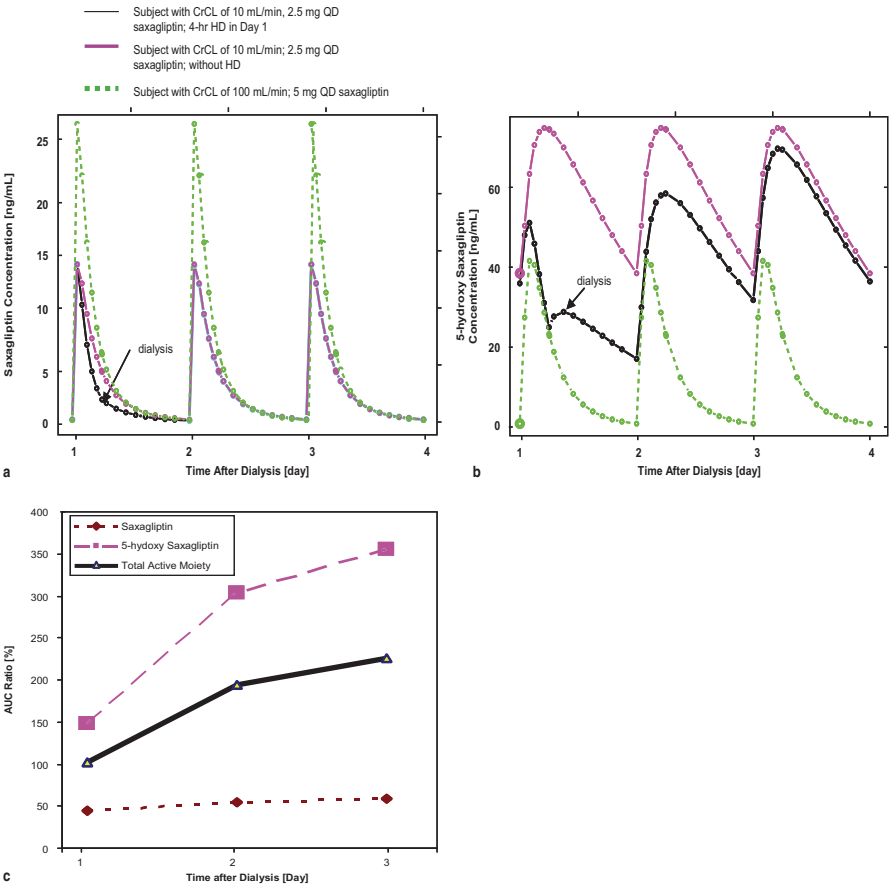

Fig. 4.6 Simulated saxagliptin (*panel a*) and 5-hydroxy saxagliptin (*panel b*) concentrations in subjects with creatinine clearance (CrCL) of 10 mL/min receiving 2.5 mg once daily saxagliptin with or without 4-h HD session starting at 2-h post-dose on day 1, and in subjects with CrCL of 100 mL/min receiving 5 mg once daily saxagliptin. Simulated steady state area under curve (*AUC*) ratio (*panel c*) between subjects with CrCL of 10 mL/min receiving 2.5 mg once daily saxagliptin and 4-h HD session on day 1 vs. subjects with CrCL of 100 mL/min receiving 5 mg once daily saxagliptin. (Zhang et al. 2012a)

including regimens that were never clinically tested. This case study is intensively discussed later in this chapter. In addition to the predictions of dug exposure under conventional HD regimens, simulations can also be performed to predict drug PK profiles under alternative treatment scenarios, such as novel dialysis modalities (e.g., daily short HD instead of three-time weekly dialysis for 4 h each). These successful applications of pharmacometrics to saxagliptin and other drugs demonstrated its utility in the development and review of new therapeutics.

4.3.3 Quantify the Impact of Dialysis on Endogenous Molecules

Similar pharmacometric approaches have also been applied to quantify the impact of dialysis on endogenous molecules and offer the potential of guiding and fine-tuning dialysis prescriptions. Individualized Bayesian urea kinetic modeling (IBKM) has been recently introduced (Pfister et al. 2004). The IBKM method is proposed as a potential method to quantify and predict HD adequacy. The IBKM method can also be used to continuously adjust and optimize individual HD treatment in both adults and children (Marsenic et al. 2010). Based on a Bayesian framework, IBKM is a model-based approach that can predict equilibrated post-rebound BUN concentration using only BUN measures pre-HD and immediately post-HD. In addition, IBKM is able to assess and project individual urea kinetic parameters and profiles for various HD schedules, takes inter-compartmental clearance into account, and can incorporate individual patient data, such as dry weight (Fig. 4.7).

The IBKM method has the potential to be useful at the bedside to inform and guide individual HD prescriptions, particularly when a patient receiving long conventional HD is transitioned to daily ultrashort or nocturnal dialysis (Fissell et al. 2012). Finally, such Bayesian kinetic modeling approach offers the possibility of testing the clearance of solutes other than urea, such as β2-microglobulin and phosphorus.

4.3.4 Evaluate and Fine-Tune Dialysis Treatment in Adults and Pediatrics

Incorporating urea rebound using equilibrated urea concentration (C_{eq}) after a HD session is essential for accurate assessment of HD efficiency. It is impractical to measure C_{eq} in clinical settings, and there are no recommended methodologies to predict C_{eq} in children. The objective of this work is to assess the ability of an IBKM for predicting C_{eq} in children on HD. Developed based on adult HD data, the IBKM is a two-pool urea kinetic model that calculates Bayesian estimates of individual C_{eq}. Blood urea nitrogen (BUN) samples from 30 HD sessions in 13 children (age 12-18 years) were taken at pre-HD, immediately post-HD, and 60 min post-HD (C_{eq}). The IBKM was fitted to the observed data to predict C_{eq}. In comparison with observed C_{eq} (9.5 ± 3.8 mmol/L), the average individual predicted C_{eq} was 9.4 [± 3.8] mmol/L, with absolute individual prediction error of 6.2 ± 4.4%. For a given dialysis goal and desired dialysis duration, the required blood flow rate and dialyzer size are predicted by IBKM (Fig. 4.8) and confirmed by the analysis data. This study suggests that the IBKM can be applied in a pediatric HD setting and accurately predict C_{eq} in children using only pre- and immediately post-HD BUN. The IBKM provides a promising approach to assess HD efficiency and its optimal prescription in adults and children; it would be an obvious choice to forecast the

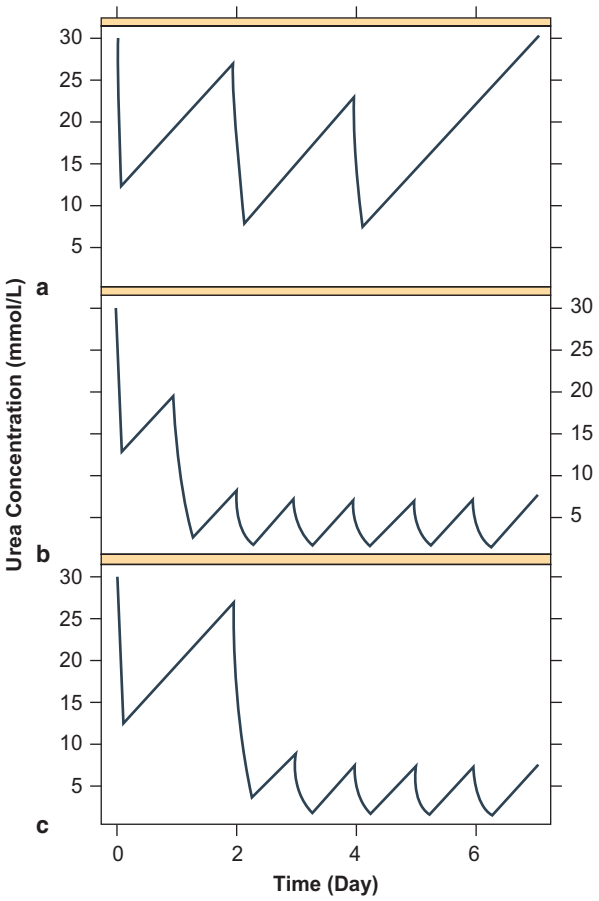

Fig. 4.7 Projected urea kinetic profiles for a patient who is planning to transition from conventional hemodialysis (CHD, three times weekly for 4 h each; *panel a*) to frequent nocturnal HD (five times weekly for 6 h each) 1 day (*panel b*) and 2 days (*panel c*) after the CHD session

removal of solutes other than urea (e.g., creatinine, uric acid) and medications in individual patients as well.

The variables considered are dialyzer size (mass/transfer coefficient, Ko; membrane area, A), blood flow, and treatment time. For an individual with pre-dialysis weight of 40 kg and BUN concentration of 30 mmol/L, the BUN concentrations during the dialysis are simulated with dialyzer mass transfer area coefficient (KoA) KoA ranging from 400 to 800 mL/min, and blood flow ranging from 150 to 300 mL/min. The time to reach 75% urea reduction ratio (% URR) are obtained from the simulation and used in constructing the plot. The lines in the contour plots indicate the time to reach 75% URR for a given combination of dialyzer KoA and blood flow. Dialyzer KoA from three commonly used dialyzers (F4HPS, F5HPS, and Gambro 14S) are indicated in the plot for illustration purpose.

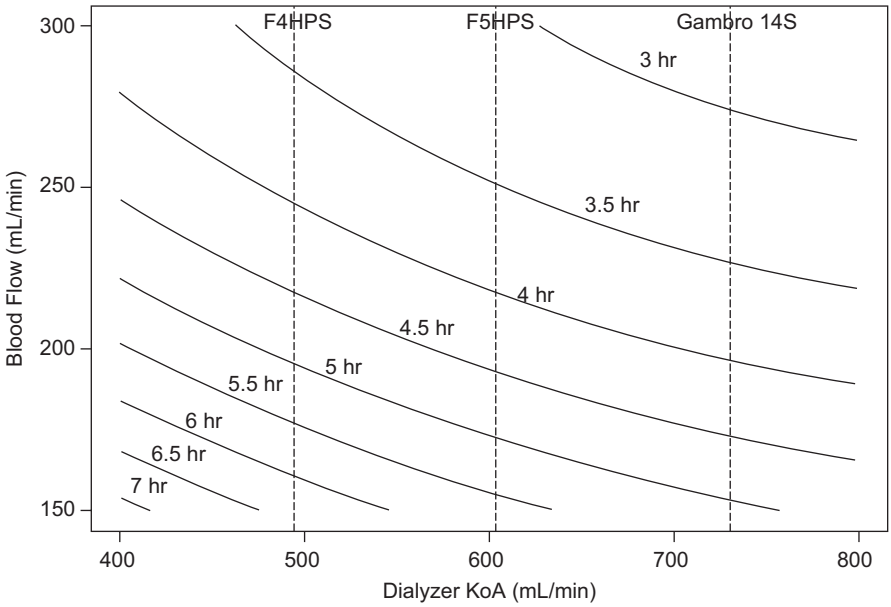

Fig. 4.8 Individual dialysis efficiency as a function of dialysis variables

4.3.5 Characterize Exposure-Response in Kidney Transplant Patients

Given the complexities of Calcineurin inhibitor (CNI)-containing immunosuppressive therapies, there is an increasing interest in CNI-free or sparing-treatment regimens (Giessing et al. 2007), and alternatives to CNI, such as CTLA-4 Ig (El-Charabaty et al. 2012). One of the difficulties of determining a therapeutic window is that it is not ethical to do a true dose-ranging study that includes suboptimal doses. Recently, model-based analyses of pooled data from phase 2 and 3 studies were employed to determine the clinical pharmacology profile of belatacept, a CTLA4-4 fusion protein, and to support dose recommendations based upon exposure-response of efficacy (control of acute rejection) and safety (serious infections and risk of lymphoproliferative events) (Zhou et al. 2012). Belatacept dose amount and frequency are highest during induction of immunosuppression in the peri-transplant period, and the dose intensity is gradually decreased to the currently recommended maintenance dose regimen of 5 mg/kg every 4 weeks, starting at the end of week 16 (Belatacept Prescribing Information (US FDA) [Internet] 2013). Belatacept exposures are therefore highest during the 3 months post-transplantation when the risk of acute rejection is greatest, and steady-state exposures are not reached until after the start of the maintenance period. A time-to-event exposure-response analysis was employed to characterize the efficacy of belatacept, to account for the time-varying nature of the belatacept exposures and of the risk of acute rejection. As shown in

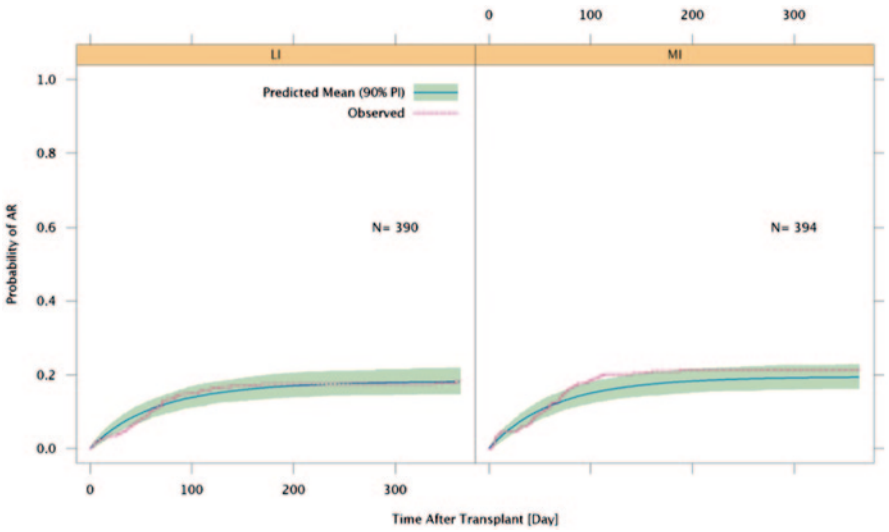

Fig. 4.9 Belatacept exposure-response of efficacy (probability of acute rejection (AR); Zhou et al. 2012). Visual predictive check of the time-to-acute rejection with less intensive (*LI*) and more intensive (*MI*) dosing regimens

Fig. 4.9, the risk of an acute rejection decreases dramatically after 3-months post-transplant, thereby justifying decreased doses of immunosuppressive agents for maintaining prophylaxis of graft rejection.

4.3.6 Quantify Impact of Drug Non-adherence on Kidney Transplant

Lack of adherence to immunosuppressive drugs, given post-transplant, is a serious problem, the prevalence of which does not appear to have changed very much over the past 30 years. A recent study found that approximately 26% of renal transplants were non-adherent to their prescribed immunosuppressive medication (Schmid-Mohler et al. 2010), which is consistent with the median non-adherence of 22% reported in a comprehensive review of the studies published between 1980 and 2001 (Butler et al. 2004). As noted above, therapeutic drug monitoring (TDM) is required for many immunosuppressive drugs due to their narrow therapeutic windows (Schiff et al. 2007; Kuypers et al. 2010). Prolonged exposure to drug levels above or below the therapeutic range is known to be associated with excess toxicity or reduced efficacy. However, the impact of transient deviations from the therapeutic window is less obvious.

A novel model-based analysis was employed to quantify the impact of non-adherence on clinical outcomes by developing and applying a model for non-adherence to CsA to predict variability in drug exposure, which was then linked to outcomes (Maclean et al. 2011). Specifically, a drug adherence model was developed to describe the drug adherence behavior of patients who were categorized according

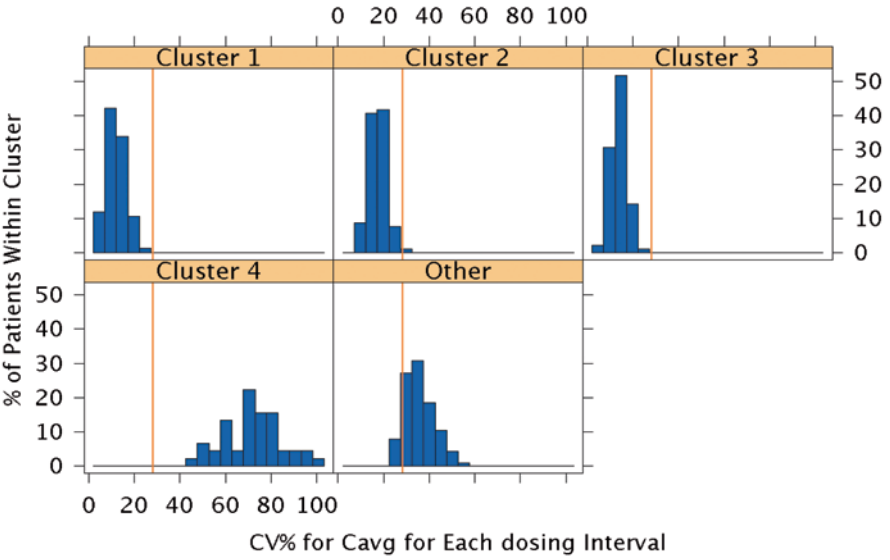

Fig. 4.10 Distribution of cyclosporin time-averaged trough concentration (*Cavg*) variability in kidney transplant patients, by adherence behavior category (**Cluster 1**: patients who almost always took their medication on time; **Cluster 2**: sometimes missed doses or were late, **Cluster 3**: frequently late in taking doses, **Cluster 4**: often missed both doses, and **Cluster 5***:* all other behaviors). The *vertical line* represents the threshold of 28 % CV in *Cavg,* above which chronic rejection rates and health-care costs are higher

to the following five previously reported clusters (Russell et al. 2006): Cluster 1 (32 %), patients who almost always took their medication on time; Cluster 2 (18 %), sometimes missed doses or were late; Cluster 3 (14 %), frequently late in taking doses; Cluster 4 (9 %), often missed both doses; and Cluster 5 (27 %), other. Specifically, the drug adherence model described the frequency with which the morning and evening doses were taken on time, late/early, or missed. The drug adherence model was applied together with a PK model of CsA (Lukas et al. 2005), to predict variability in CsA exposures, which was then linked to clinical outcome based on previously reported associations between variability in CsA exposure and long-term renal function, chronic rejection, and health-care costs based on logistic regression and receiver operating curve analysis (Waiser et al. 2002; Kahan et al. 2000). As shown in Fig. 4.10, the within patient variability in time-averaged trough concentration (Cavg) of patients in Clusters 1, 2, and 3 did not exceed level of variability associated with poor outcomes (30-36 % coefficient of variation CV), and therefore the occasional non-adherence characterized by Clusters 2 and 3 are not expected to have an impact on clinical outcome. In contrast, all patients in Clusters 4 had CV higher than the thresholds associated with poor outcome, and approximately 76 % of the patients in Cluster 5 had a CV greater than 30 %, suggesting that subjects in these groups were at high risk for having poorer outcomes.

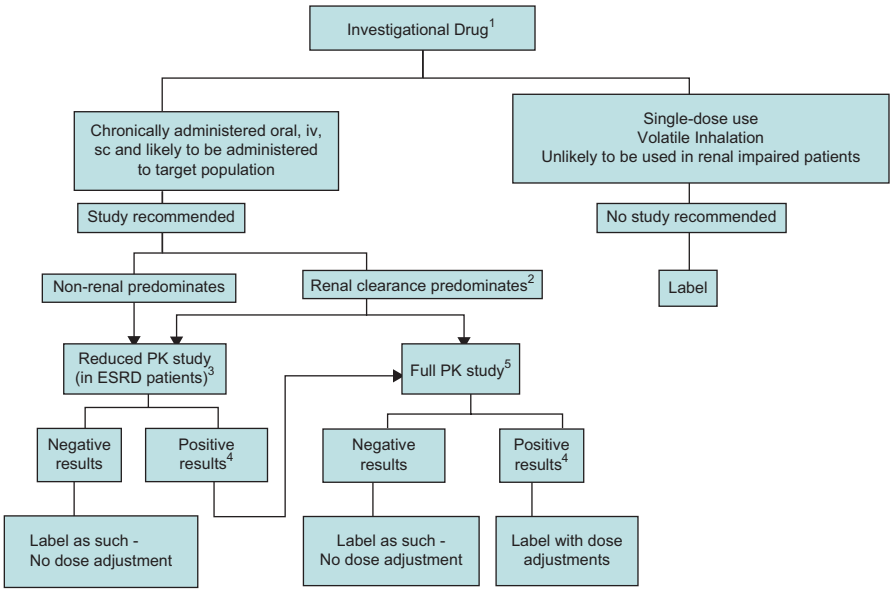

Fig. 4.11 Decision tree for use in determining when a study in subjects with impaired kidney funtion is appropriate (Draft Guidance: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet] 2010). *1* Metabolites (active/toxic) follow the same decision tree. *2* The sponsor has the option of conducting a reduced study in end-stage renal disease (ESRD) patients or a full study. *3* To be conducted in ESRD patients not yet on dialysis. *4* The results are "positive" when pharmacokinetic (PK) changes are clinically significant based on exposure-response of the drug. *5* See guidance for the full PK study design, or additional studies can be conducted including a population PK evaluation

4.3.7 Evaluate and Fine-Tune Therapeutic Doses for CKD

The FDA encourages to (1) understand multitude of interrelated factors that can affect systemic exposure and response, (2) carefully design trials in subjects with impaired kidney disease, and (3) apply quantitative pharmacometric methods for characterizing drug exposure and evaluating in therapeutic doses in subjects with impaired kidney (Fig. 4.11; Draft Guidance: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet] 2010; Huang et al. 2009; Zhang et al. 2012b). Compared to the 1998 FDA guidance, there are three new recommendations in the 2010 FDA draft guidance "Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling": (1) PK studies in patients with impaired kidney function are conducted for drugs that are eliminated via non-renal route, in addition to those via renal route (Fig. 4.11), (2) staging of kidney function be conducted using the eGFR (e.g., the four-parameter modification of diet in renal disease (MDRD) equation), in addition to the C–G equation, and (3) conduct of studies in HD patients be performed during dialysis (on dialysis) and inter-dialysis (off dialysis) periods.

Table 4.4 Hazard ratio and 95% confidence interval (CI) for stroke/systemic embolic event (SEE) and major bleeds comparing dabigatran etexilate (DE) 150 mg twice daily to warfarin by kidney function. (Hariharan and Madabushi 2012)

Creatinine clearance, mL/min	Fold increase in dabigatran trough plasma concentration in RE-LY	Hazard ratio (95% CI) for stroke/SEE, DE 150 mg vs Warfarin	Hazard ratio (95% CI) for major bleeds, DE 150 mg vs Warfarin
Moderate, 30≤ and <50	2.29	0.46 (0.29–0.73)	0.97 (0.74–1.27)
Mild, 50≤ and <80	1.47	0.67 (0.49–0.91)	0.88 (0.71–1.07)
Healthy, ≥80	1.00	0.71 (0.44–1.15)	0.81 (0.59–1.11)

RE-LY Randomized Evaluation of Long-term Anti-Coagulant Therapy

To optimize drug therapy for individuals and subgroups, it is critical to understand how various intrinsic (e.g., age, gender, race, genetics, organ impairment) and extrinsic factors (e.g., diet, smoking, concomitantly administered drugs) affect drug exposure, dosing, and response. PK data in subjects with impaired kidney function are used to determine appropriate drug dosing in subjects with impaired kidney function in comparison to subjects with normal kidney function. Besides being evaluated in dedicated PK studies, the effect of impaired kidney function on a drug's PK can also be evaluated in phase 2 or phase 3 clinical studies with sparse PK sampling if a sufficient number of patients with various degrees of renal impairment is included in these studies. Pharmacometric analyses can help rationalize a need for dosage adjustment in this specific population based on exposure–response relationship of the drug.

For example, dabigatran represents one of the recent instances where renal function influenced dosing decisions (Hariharan and Madabushi 2012; Lehr et al. 2012). Dabigatran etexilate mesylate, a direct oral thrombin inhibitor, was approved by the FDA in October 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The pivotal efficacy trial supporting the approval, randomized evaluation of long-term anticoagulant therapy (RE-LY), compared two blinded doses of dabigatran, 110 mg and 150 mg, with open-label warfarin (Table 4.4). Based on the efficacy (reduction in incidence of stroke and systemic embolism) and safety (bleeding risk) findings, the FDA-approved dabigatran 150 mg given orally twice daily in patients with CrCL>30 mL/min. The FDA also approved dabigatran 75 mg administered twice daily in patients with severe renal impairment (defined as CrCL between 15 and 30 mL/min).

To ensure that subgroups with severe impaired kidney function would have access to an appropriate dose of dabigatran, a pharmacometric approach was applied to evaluate dosing regimens of interest in 'virtual' subjects with various levels of kidney function. Results from model-based simulation of various doses of interest indicated that (1) a dosing regimen of 150 mg QD leads to significantly higher average exposures beyond the range studied in RE-LY, (2) a dosing regimen of 75 mg QD regimen results in lower average exposures and was considered to be less effective for stroke reduction, and (3) a dosing regimen of 75 mg twice daily is the preferred dose for subjects with severely impaired kidney function as it provides similar exposures to that expected in subjects with moderately impaired kidney function, for whom a 150-mg twice-daily regimen produced substantial benefit in pivotal clinical trials.

In another case, a pharmacometric approach was applied to quantify apixaban's therapeutic utility in prevention of venous thromboembolism in subjects with normal or moderately impaired kidney function (Leil et al. 2010). A therapeutic utility index (TUI) was assessed by integrating efficacy and safety predictions to quantify apixaban's efficacy/safety balance as a function of steady-state AUC. Of the apixaban dosage regimens tested in phase 2, the 2.5-mg twice-daily dosage regimen had the highest TUI (86.2%). This was also higher than the TUI for either 30-mg twice-daily enoxaparin (82.5%) or for warfarin (71.8%). Difference in apixaban's TUI in subjects with moderately impaired kidney function and those with normal kidney function was marginal indicating that dose adjustment is not needed in subjects with mild or moderate impairment of kidney function.

4.3.8 Enhance Drug Label for CKD

There are several additioned examples where pharmacometric approaches, including physiologically based modeling and simulation (in conjunction with well-designed studies) were used to characterize CKD-related changes in drug exposure and optimize dose selection in CKD: amikacin (De Cock et al. 2012) argatroban (Madabushi et al. 2011), fondaparinux (Turpie et al. 2009), gentamicin (Lanao et al. 1989), panipenem/betamipron (Tajima et al. 2006), pefloxacin (Bruno et al. 1991), piperacillin/tazobactam (Tornøe et al. 2007), ribavirin (Bruchfeld et al. 2002), and telbivudine (Zhou et al. 2009).

Model-based trial simulation can predict drug exposures for alternative dosing regimens, compare simulated drug exposures with a predefined target range (i.e., therapeutic window), and thus identify doses that produce safe and efficacious concentrations in a large portion of patients (i.e., 75% of subjects). This quantitative approach was applied to optimize dosing of entecavir in subjects with CKD (Bifano et al. 2010). Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady state ranging from 62 to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 mL/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion. The PK of entecavir following a single 1-mg dose were studied in 34 subjects (without chronic hepatitis B virus infection) with various degrees of impaired kidney function, including subjects whose CKD was managed by HD or continuous ambulatory peritoneal dialysis (CAPD). In subjects with CKD, the apparent oral clearance of entecavir decreased as creatinine clearance decreased.

A pharmacometric approach was applied to (1) characterize the relationship between a measure of kidney function (CrCL) and apparent oral clearance of entecavir, (2) simulate steady-state exposure of entecavir for various alternative dose regimens, (3) calculate the fraction of subjects with exposure of entecavir within a predefined target range, and (4) identify dose regimens that produce target exposure levels in 75% or more subjects with normal and reduced kidney function. Output from this model-based simulation indicated that the following dose adjustments (percentage of starting dose) provide consistent steady-state exposures in subjects

Table 4.5 Recommended dosage of entecavir (BARACLUDE) in subjects with CKD

Creatinine clearance (mL/min)	Usual dose (0.5 mg)	Lamivudine—refractory or decomposed liver disease (1 mg)
≥50	0.5 mg once daily	1 mg once daily
30-<50	0.25 mg once daily[a] *OR* 0.5 mg every 48 h	0.5 mg once daily *OR* 1 mg every 48 h
10-50<30	0.15 mg once daily[a] *OR* 0.5 mg every 72 h	0.3 mg once daily[a] *OR* 1 mg every 72 h
<10 Hemodialysis[b] or CAPD	0.05 mg once daily[a] *OR* 0.5 mg every 7 days	0.1 mg once daily[a] *OR* 1 mg every 7 days

[a] For doses less than 0.5 mg. BARACLUDE Oral Solution is recommended
[b] If administered on a hemodialysis day. administer BARACLUDE after the hemodialysis session

with impaired kidney function: mild impairment (no adjustment, 100%), moderate impairment (50%), severe impairment four (30%), and subjects on dialysis (20%). These results provided a quantitative rational for a detailed dose recommendation in the drug label (Baraclude Prescribing Information. US Food and Drug Administration [Internet] 2012):

> Dosage adjustment is recommended for patients with creatinine clearance less than 50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in Table 4.5 (Baraclude Prescribing Information. US Food and Drug Administration [Internet] 2012). The once-daily dosing regimens are preferred.

4.4 Opportunities for Pharmacometrics in CKD

Pharmacometric approaches are useful to characterize drug effects on kidneys and effects of kidneys on drugs. Current pharmacometric activities are focused on individual compounds for their search, prevention, and treatment of CKD. Examples of the applications include: (1) assess and compare efficacy/safety profiles of entire drug classes with model-based meta-analyses (e.g., effects of ACE inhibitors, ARBs, and renin inhibitors on hypertension, proteinuria, *and* GFR in CKD), (2) characterize relationships between biomarkers/imaging endpoints and clinical endpoint (e.g., relationships between changes in total kidney volume (TKV) and GFR in polycystic kidney disease), (3) develop disease progression models to project long-term cardiovascular and CKD outcomes (e.g., relationships between proteinuria and GFR and time to RRT in T2DM subjects with CKD), (4) optimize design of clinical trials in subjects with CKD (in conjunction with new regulatory guidance documents), and (5) evaluate new metrics for novel dialysis modalities to further optimize RRT in adults and pediatrics (e.g., use bedside computer models to evaluate, monitor, and fine-tune "dose" of dialysis).

A sustained collaborative effort between key stakeholders involved in research, development, and use of medicines in CKD, is required to bring pharmacometrics to its full potential. Initiatives such as the C-Path consortium (Critical Path Institute [Internet] 2013) and the Drug Disease Model Resources (DDMoRe) consortium (DDMoRe: Innovative Medicines Initiative [Internet] 2013) can advance pharmacometrics and facilitate scientific partnerships between academic institutes, biotech/pharma companies and societies such as the International Society of Nephrology (International Society of Nephrology (ISN) Gateway [Internet] 2013) and the International Society of Pharmacometrics (ISoP International Society of [Internet] 2013).

The Polycystic Kidney Disease (PKD) Outcomes consortium is an example of a successful collaboration between Critical Path Institute (C-Path), the PKD Foundation (PKD Foundation [Internet] 2013), Clinical Data Interchange Standards Consortium (CDISC), and four leading academic medical centers (Tufts University, University of Colorado—Denver, Emory University, and Mayo Clinic). Autosomal dominant PKD (ADPKD) is a debilitating genetic disease affecting more than 600,000 Americans and 12 million people worldwide and for which there is currently no known cure or effective treatment (Helal et al. 2012).

The primary goals of the PKD Outcomes consortium are to use and model clinical data from ADPKD patients to characterize the relationship between early changes in TKV and long-term CKD outcomes, and support the regulatory qualification of TKV as an accepted measure for assessing the progression of ADPKD in clinical trials, with the ultimate goal to facilitate development and approval of new medicines for subjects with ADPKD. Similar efforts are needed for other kidney diseases such as Fabry nephropathy.

Innovative pharmacometric approaches for facilitating research, development, and use of new medicines will help us to fight the silent, deadly kidney disease.

4.5 Take-Home Messages

- Know that CKD is a common and deadly disease
- Use eGFR rather than creatinine clearance to stage CKD
- Understand how drugs can affect kidneys and how kidneys can affect renal and non-renal elimination of drugs and response to drugs
- Apply pharmacometric approaches (including semi-mechanistic models) to characterize relationships between measures of kidney function and drug exposure-response
- Utilize model-based simulations to optimize dose regimens and enhance drug labels for CKD
- Innovate pharmacometric approaches to evaluate and fine-tune RRT by dialysis or transplantation
- Facilitate partnerships between academic institutes, biotech/pharma companies and scientific societies to fight the silent, deadly kidney disease

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