



## Medication Safety Principles and Practice in CKD

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### Abstract

Ensuring patient safety is a priority of medical care because iatrogenic injury has been a primary concern. Medications are an important source of medical errors, and kidney disease is a thoroughfare of factors threatening safe administration of medicines. Principal among these is reduced kidney function because almost half of all medications used are eliminated *via* the kidney. Additionally, kidney patients often suffer from multimorbidity, including diabetes, hypertension, and heart failure, with a range of prescribers who often do not coordinate treatments. Patients with kidney disease are also susceptible to further kidney injury and metabolic derangements from medications, which can worsen the disease. In this review, we will present the key issues and threats to safe medication use in kidney disease, with a focus on predialysis CKD, as the scope of medication safety in ESKD and transplantation are unique and deserve their own consideration. We discuss drugs that need to be avoided or dose modified, and review the complications of a range of medications routinely administered in CKD, as these also call for cautious use.

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### Introduction

Moliere, the 17th century playwright wrote, “Nearly all men die of their remedies, and not of their illnesses.” Many therapeutic drugs used as remedies are kidney-relevant, meaning they require clearance or metabolism by the kidney or have potential for nephrotoxicity (1,2). One important barrier to medication safety is CKD is often under-recognized (3,4). Failure to recognize patients with CKD is a lost opportunity to minimize patient safety threats related to medications. A study alerting providers of medication orders requiring modifications because of impaired kidney function revealed 14% of all orders were for kidney-relevant medications (5). Of these, about 15% were flagged with an initial prescription error. Others have found a higher proportion of medication orders with potential nephrotoxicity, or orders not properly modified for kidney function, which are therefore associated with high risk of adverse events for both kidney-relevant and nonkidney-relevant medications in CKD (6,7).

Adverse medication-related outcomes in CKD can be classified as those leading to kidney damage, including AKI, accelerated kidney function loss, and ESKD, as well as other metabolic complications, including hyperkalemia, hypercalcemia, hypoglycemia, and bleeding, among others (8). Omitted therapies, such as failure to initiate erythropoiesis-stimulating agents (ESAs) for severe anemia, can also be considered safety events. A substantial proportion of the burden of illness in patients with CKD relates to such safety complications, and may be prevented with improved attention to this population’s special care needs.

Safe medication use in CKD is a complex process involving determination of kidney function, consideration of changes in drug pharmacokinetics (PK) and

pharmacodynamics (PD) as kidney function declines, and judicious use of therapies to manage uremic complications and other comorbid conditions (9).

The US Food and Drug Administration (FDA) guidance for dosing recommendations accounting for kidney function were not issued until 1998. Although initial FDA guidance called for direct measurement of GFR using a tracer such as iothalamate, the 2000s witnessed the validation and implementation of estimating equations to assess kidney function (9). Yet, estimates of kidney function on the basis of creatinine clearance (*e.g.*, the Cockcroft–Gault equation) and GFR (*e.g.*, the CKD Epidemiology Collaboration equation) can differ substantially from direct measurement of kidney function. These discrepancies can lead to misguided dosing recommendations for certain drugs (10). However, direct measurement of kidney function is often not practical; hence, a Kidney Disease Improving Global Outcomes (KDIGO) consensus panel recommended that clinicians’ refer to a valid equation for determination of eGFR (9). Dosing adjustments should be made on the basis of clinically observed drug response and toxicity, as well as drug levels, when measurable.

Altered drug PK/PD profiles in CKD may warrant modified dosing or drug discontinuation (8,9,11). Drug absorption in the gastrointestinal (GI) tract may be impaired by medications that alter gastric pH (*e.g.*, proton pump inhibitors) and comorbid conditions that cause edema (*e.g.*, congestive heart failure [CHF]) or GI losses common in CKD (*e.g.*, diarrhea) (11). The volume of distribution of water-soluble drugs may also be increased in the setting of edema. Uremia in CKD can also alter the volume of distribution of plasma/tissue protein-bound drugs,

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which can significantly affect therapeutic and safety outcomes of narrow therapeutic range medications (*e.g.*, digoxin) (11). Changes in hepatic or nonrenal clearance of commonly used medications, such as antibiotics and antihypertensives, have also been observed in CKD (12). All mechanisms of kidney excretion are impaired in CKD, including glomerular filtration, tubular secretion, and reabsorption (11). Progressive decline in kidney function results in changes in clearance, therapeutic effect, and risk of toxicity of many drugs eliminated through the kidneys.

### Medication Safety in CKD and Related Complications

In addition to a medication's nephrotoxic effects, patients with CKD are also susceptible to other adverse effects with agents routinely used in the management of CKD and comorbid conditions. Examples include anticholinergic (*e.g.*, histamine-1 receptor antagonists), sedative (*e.g.*, codeine, diazepam), and hypoglycemic (*e.g.*, glyburide) effects, as well as electrolyte abnormalities (*e.g.*, renin-angiotensin-aldosterone system [RAAS] blockers, sulfamethoxazole-trimethoprim, mineralocorticoid receptor antagonists, calcium- and magnesium-containing antacids). Agents with particular pertinence to patients with CKD are discussed below.

#### Diuretics

Thiazide and loop diuretics are commonly used for natriuresis and BP control with a reduced GFR. This is especially important in advanced CKD, where extracellular volume excess is a concern and BP becomes more salt-sensitive. Loop diuretics are the preferred agents at GFR < 30 ml/min per 1.73 m<sup>2</sup>, but more potent thiazide diuretics also can be used, often in combination with loop diuretics. Injudicious diuretic use can increase the risk of AKI in vulnerable patients with CHF, ascites, or other edematous states, especially with superimposed volume depletion (13). Loop and thiazide diuretics are also associated with a range of electrolyte disturbances, including hypokalemia, hypomagnesemia, and hypochloremic metabolic alkalosis (14,15). Additional metabolic derangements include hyperuricemia, and at higher doses of thiazide diuretics, glucose intolerance and hyperlipidemia (13).

#### RAAS Blockers as a Double-Edged Sword

RAAS blockers are essential to CKD treatment and although not overtly nephrotoxic, under certain clinical circumstances they have the potential for harm (16). Practitioners may construe physiologic reductions in GFR with RAAS blockers as justification to avoid these agents with advanced CKD; however, RAAS blockers have demonstrated benefit in early as well as later stages of CKD (17). Hazards from RAAS blockers are most prominent in conditions where the kidney is autoregulation-dependent, including CHF, active diuresis, and other illnesses with attendant volume depletion (16).

Hypotension with RAAS blockers is common among elderly patients, and episodes of AKI across the range of severity are not infrequent among nursing home patients treated with RAAS blockers (16,18). AKI is also more common with treatment with RAAS blockers during high summer temperatures and with volume depletion, and can also occur with bilateral renal artery stenosis or unilateral

stenosis with a solitary kidney (19). Patients with CHF on angiotensin-converting enzyme inhibitors develop a greater rate of AKI with intensified diuretic regimens than their counterparts on lower doses or no diuretics (20). Adding a nonsteroidal anti-inflammatory drug (NSAID) to an RAAS blocker and diuretic can amplify the risk of AKI, and has been described as a "triple whammy." (21) Similar conditions may increase the risk of AKI when more than one RAAS blocker are used together, or in combination with sodium-glucose cotransporter 2 in patients with CKD and diabetes (22,23). An increase in AKI admissions have been reported and correspond with a rise in RAAS blocker prescriptions across geographic regions. AKI admissions increased as much as 15% because of an increase in RAAS blocker prescriptions (24).

#### Dyskalemia

Hyperkalemia and hypokalemia are common safety concerns for patients with CKD because they can lead to altered cardiac electro-conduction, arrhythmias, and sudden death (25–30). Hyperkalemia can occur with RAAS blocker use, especially when two are used in combination, or with other drugs including potassium-sparing diuretics, NSAIDs, or trimethoprim-sulfamethoxazole (31). Less commonly, heparin can cause hyperkalemia in the setting of AKI, or when used with other agents that increase the risk of hyperkalemia (32). It is also important to note that hypokalemia can develop with unsupervised diuretic use (33).

Several tactics in response to hyperkalemia can shift potassium from the extracellular to intracellular space (*e.g.*, insulin and glucose,  $\beta$ -agonist therapy, and bicarbonate in the setting of acidosis), but definitive therapies remove total body potassium. These treatments include diuresis, which may have limited effectiveness and the potential for metabolic or hemodynamic complications. Cation exchange resins, such as sodium polystyrene sulfate, have limited evidence for efficacy in potassium removal, and have associated concerns for toxic effects including bowel necrosis (34). However, this complication is uncommon, with unclear linkage to oral versus rectal administration (35). The cation exchange resin patiromer has introduced an alternative for chronic treatment of hyperkalemia, and can be used in conjunction with RAAS blockers (36). However, patiromer has been associated with hypomagnesemia and altered absorption of some common drugs (37). Mineralocorticoid agonists may have modest effectiveness in reducing serum potassium, especially in hyperkalemic patients on dialysis (38). Dialysis remains the gold standard for potassium removal, but should be used sparingly, except for patients with ESKD (25). Treatment and prevention of hypokalemia includes reduction in diuretic use, sodium restriction, and liberalization of patients' diets to include potassium-rich foods. Consideration of potassium-sparing diuretics and RAAS blockers, where appropriate, should also be considered (33).

#### Treatments for Anemia in CKD

Anemia management in CKD is a balance between optimizing erythropoiesis and minimizing adverse effects associated with therapeutic agents that treat anemia (39,40). Use of ESAs along with iron supplementation to

treat anemia are important elements in CKD care (40). Despite extensive experience with these agents, many questions remain regarding optimal and safe therapeutic end points (39–41).

Iron supplementation (oral or intravenous) is usually the first step in anemia management (40,42). However, oral iron use is often limited because of suboptimal efficacy and GI intolerance (43,44). Intravenous iron is more efficacious at correcting iron deficiency, improving hemoglobin levels, and reducing ESA use and blood transfusions, but is often underutilized because of clinician apprehension of infusion-related reactions and iron overload (42,43). Anaphylaxis most commonly occurs with high molecular weight iron dextran, whereas severe or life-threatening reactions are rare with nondextran formulations, such as iron sucrose and sodium ferric gluconate complex (42,45). Commentaries have postulated that aggressive iron supplementation and overload in conjunction with ESA use may increase the risk of safety events (46). The upper limits of iron stores is clinically undefined, but studies suggest that adverse effects related to iron overload are not likely to occur at ferritin levels below 1200–2000 ng/ml (42,45). However, the KDIGO guidelines take a conservative stance with regard to upper limits of iron stores, and do not recommend routine use of iron supplementation when transferrin saturation and ferritin levels are adequate (40).

Controversy continues over appropriate ESA use, and there are safety concerns about optimal treatment targets in CKD (47–50). Generally, trials evaluating aggressive treatment targets with epoetin alfa have been successful at achieving hemoglobin targets, but demonstrate a higher rate of arteriovenous fistula thrombosis, myocardial infarction, death, and CHF-related hospitalizations. Comparable results have been reported with darbepoetin alfa (48). Apart from a modest improvement in quality of life with higher hemoglobin targets, aggressive treatment has been associated with an increased risk of stroke, venous thromboembolism, and death in patients with an active malignancy (40). Hence, the benefits of targeting higher hemoglobin levels with ESAs are limited by significant toxicity signals (50,51). As part of best practices identified by the American Society of Nephrology's "Choosing Wisely" campaign, an individualized patient approach to ESA use is recommended to alleviate symptoms while maintaining conservative hemoglobin targets and minimizing the need for transfusions (52). Specifically, ESAs should be avoided in asymptomatic patients who are predialysis, with hemoglobin levels  $>10$  g/dl. When treatment is warranted, ESAs should be used judiciously, along with close monitoring of hemoglobin and anemia symptoms.

### Treatments for CKD–Mineral and Bone Disorder

CKD–mineral and bone disorder (CKD–MBD) is a complex condition characterized by phosphate, calcium, vitamin D, and parathyroid hormone (PTH) abnormalities (53). Pharmacotherapeutic interventions have primarily focused on correcting laboratory disturbances with the intent of reducing long-term complications. Paradoxically, drug therapy for CKD–MBD has the potential to accelerate disease progression if not used appropriately.

Maintaining phosphorus and calcium homeostasis in CKD is associated with decreased kidney and cardiovascular risk (54). Phosphate binders are the recommended first-line therapy in CKD to correct hyperphosphatemia

(55). However, binders do not significantly improve phosphorus levels or delay the progression of coronary artery calcification in the predialysis CKD population (56–59). The updated 2017 KDIGO guidelines de-emphasize targeting precise calcium and phosphate levels, but endorse the initiation and adjustment of therapy on the basis of "persistent and progressively" abnormal individual levels in the context of overall trends in CKD–MBD biomarkers (55,57).

Noncalcium-based binders may have less effect on calcium balance and cardiovascular endpoints (60). Specifically, novel iron-based phosphate binders are effective alternatives to managing hyperphosphatemia and minimizing risk of hypercalcemia, and have an added benefit of improving iron stores (61). When cost limits choice to calcium-based binders, the dosing should be tailored to the individual patient's dietary calcium intake to maintain a neutral calcium balance (59). Calcium-containing binders should be considered primarily in patients with CKD with low calcium intake. Calcium-based products should be avoided in patients with adequate (800–1000 mg/d) or excessive intake. Examples of surreptitious calcium intake include over-the-counter antacids, and patiromer used in the treatment of hyperkalemia.

Calcitriol and other vitamin D receptor antagonists (VDRA) suppress parathyroid gland activity in advanced stages of CKD (55). However, there may be a negative shift in the risk–benefit profile for VDRA in predialysis CKD because their use is associated with increased risk of hypercalcemia with no significant benefit to cardiac function (62). The current guidelines recommend avoiding routine use of VDRA before ESKD (55). When therapy is warranted, VDRA should be used conservatively and only with evidence that intact PTH levels are progressively and/or persistently elevated.

Calcimimetics are also efficacious at suppressing PTH secretion in CKD–MBD (55,63). This class of agents is commonly associated with hypocalcemia in patients with ESKD and patients who are predialysis, however, the clinical significance of this expected safety event is unclear (55). Calcimimetics are not recommended in CKD GFR categories 3a–5 (G3a–G5) when the patient is not on dialysis, but are limited to use in CKD category G5 when the patient is on dialysis (55). Additionally, the guidelines recommend an individualized approach to managing hypocalcemia on the basis of severity of symptoms and calcium levels.

### Antihyperglycemic Agents in CKD

Poorly controlled type 2 diabetes (T2DM) mellitus can lead to microvascular complications, including nephropathy, as  $>40\%$  of patients with T2DM have CKD (64). Slowing the progression of nephropathy through glyce-mic control is of paramount importance in clinical management.

Metformin remains the first-line treatment for T2DM, given its hemoglobin A1c lowering potential, oral administration, neutral effect on body weight, and cardiovascular outcome and all-cause mortality benefit (65). Historically, metformin was contraindicated in patients with a serum creatinine level of  $\geq 1.5$  or  $\geq 1.4$  mg/dl for men and women, respectively, given that the drug is eliminated through the kidneys and can increase the risk of lactic acidosis (66). However, this is an exceedingly rare complication and most

**Table 1. Cautionary notes for prescribing in people with CKD**

| Medication                             | Comments                                                                                                                                                                                                                                   |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Narrow therapeutic index drugs</b>  |                                                                                                                                                                                                                                            |
| Aminoglycosides                        | Nephrotoxic (acute tubular necrosis, AKI). Ototoxic. Therapeutic drug monitoring recommended.                                                                                                                                              |
| Digoxin                                | Increased for digoxin toxicity including arrhythmias. Therapeutic drug monitoring recommended.                                                                                                                                             |
| Lithium                                | Diabetes insipidus, interstitial disease. Avoid concomitant use of thiazide diuretics and NSAIDs, maintain hydration. Therapeutic drug monitoring recommended.                                                                             |
| Phenytoin                              | Low albumin will affect bound concentration. Monitor free phenytoin level.                                                                                                                                                                 |
| Tacrolimus                             | Vasoconstriction, nephrotoxicity. Avoid concomitant use of CYP 3A4 inhibitors. Therapeutic drug monitoring recommended.                                                                                                                    |
| Warfarin                               | Increased risk of bleeding. Close INR monitoring recommended.                                                                                                                                                                              |
| <b>Analgesics</b>                      |                                                                                                                                                                                                                                            |
| NSAIDs                                 | Hemodynamically mediated kidney injury, sodium and/or potassium retention, interstitial nephropathy. Avoid with concomitant use of diuretics or RAAS inhibitors, maintain hydration, consider alternate analgesic.                         |
| Meperidine                             | Active metabolite, normeperidine, increases risk of seizure. Avoid.                                                                                                                                                                        |
| Morphine                               | Active metabolites, increased drug effect.                                                                                                                                                                                                 |
| <b>Contrast agents</b>                 |                                                                                                                                                                                                                                            |
| Iodinated contrast media               | Nephrotoxic. Use lowest dose, maintain hydration with saline, can consider N-acetylcysteine or sodium bicarbonate, avoid concomitant nephrotoxins, avoid use of high-osmolarity agents, avoid use of gadolinium-containing contrast media. |
| <b>Bowel preparation</b>               |                                                                                                                                                                                                                                            |
| Phosphate-containing bowel preparation | Increased risk for phosphate nephropathy and electrolyte disturbances. Avoid phosphate-based preparations.                                                                                                                                 |
| <b>Herbals</b>                         |                                                                                                                                                                                                                                            |
| Licorice                               | Increased risk of sodium and water retention, hypokalemia, hypertension. Avoid use.                                                                                                                                                        |
| Noni juice                             | Increased risk of hyperkalemia. Avoid use.                                                                                                                                                                                                 |
| St. John's wort                        | CYP inducer. Increased risk of drug interactions. Avoid use.                                                                                                                                                                               |
| <i>Ginkgo biloba</i>                   | Increased risk of bleeding. Avoid use.                                                                                                                                                                                                     |
| Ephedra alkaloids (ma huang)           | May potentiate hypertension. Avoid use.                                                                                                                                                                                                    |

Excerpted from the 2012 Kidney Disease Improving Global Outcomes Guidelines on the management of CKD (77). NSAIDs, nonsteroidal anti-inflammatory drugs; CYP 3A4, cytochrome p450 3A4; INR, International Normalized Ratio; RAAS, renin-angiotensin-aldosterone system; CYP, cytochrome p450.

patients with mild-to-moderate kidney impairment safely tolerate metformin (66). Nonetheless, although the incidence remains low, the risk of lactic acidosis or elevated lactate concentrations increases with metformin use with declining kidney function, especially when higher doses are used. In 2016, the FDA required changes to metformin labeling to expand its use in patients with impaired kidney function (Table 1) (67). The guidelines also recommend using GFR to estimate kidney function rather than serum creatinine to determine whether a patient is a safe candidate for metformin.

The American Diabetes Association advocates considering both efficacy and safety profiles when selecting an agent to add to metformin (65). Patients with T2DM and CKD are at an increased risk for hypoglycemia, and some agents pose a higher risk of hypoglycemia than others. Sulfonylureas and insulin have a higher risk for hypoglycemia than other drug classes. Within the sulfonylurea class, glyburide is not recommended for use in CKD because it is hepatically metabolized with active metabolites excreted by the kidney (68). Glimepiride is metabolized in the liver into two major metabolites, and clinical trials have demonstrated a reduced elimination of these

metabolites with kidney impairment; therefore, to reduce the risk of hypoglycemia, the drug should be initiated at a low dose in patients with T2DM and CKD. Glipizide is also metabolized by the liver but into inactive metabolites excreted by the kidney; hence, it is the preferred sulfonylurea agent for use in CKD.

Thiazolidinediones are highly metabolized by the liver and require no dose adjustments in CKD (68). Despite this, the thiazolidinedione class of agents is often avoided because of a propensity for fluid retention and edema in CKD.

Two classes of incretins available for the treatment of T2DM have grown in use over the last decade: dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists. All dipeptidyl peptidase-4 inhibitors agents can be safely used in all stages of CKD, and ESKD on dialysis (69). Certain agents in this class are eliminated through the kidneys, such as alogliptin, saxagliptin, and sitagliptin, and require a dose adjustment with lower GFRs. Linagliptin is eliminated through a hepatobiliary route and does not require adjustment, offering an advantage over the other members in the class (70).

Each of the six available glucagon-like peptide-1 receptor agonists differ in their recommendations for use in CKD,

**Table 2. Dosing recommendations for select drug therapies by CKD stage**

| Drug Class                                                          | Drug                                                        | CKD Staging by GFR Category (ml/min per 1.73 m <sup>2</sup> ) |                    |                                  |                                |                    |                   |
|---------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------|--------------------|----------------------------------|--------------------------------|--------------------|-------------------|
|                                                                     |                                                             | Stage 1<br>(>90)                                              | Stage 2<br>(89–60) | Stage 3a<br>(59–45)              | Stage 3b<br>(44–30)            | Stage 4<br>(29–15) | Stage 5<br>(<15)  |
| Biguanide                                                           | Metformin                                                   | R                                                             | R                  | R                                | DA <sup>a</sup>                | X                  | X                 |
|                                                                     | Sulfonylureas                                               | R                                                             | R                  | R                                | R                              | R                  | R                 |
| Thiazolidinediones                                                  | Glipizide                                                   | R                                                             | R                  | R                                | R                              | R                  | C                 |
|                                                                     | Glimepiride                                                 | R                                                             | R                  | R                                | R                              | R                  | C                 |
|                                                                     | Glyburide                                                   | R                                                             | R                  | C                                | C                              | C                  | C                 |
|                                                                     | Pioglitazone                                                | R                                                             | R                  | R                                | R                              | R                  | R                 |
| DPP4 inhibitors                                                     | Rosiglitazone                                               | R                                                             | R                  | R                                | R                              | R                  | R                 |
|                                                                     | Alogliptin                                                  | R                                                             | R                  | DA                               | DA                             | DA                 | DA                |
|                                                                     | Linagliptin                                                 | R                                                             | R                  | R                                | R                              | R                  | R                 |
|                                                                     | Saxagliptin                                                 | R                                                             | R                  | R                                | DA                             | DA                 | DA                |
| SGLT2 inhibitors                                                    | Sitagliptin                                                 | R                                                             | R                  | R                                | DA                             | DA                 | DA                |
|                                                                     | Canagliflozin                                               | R                                                             | R                  | DA                               | X                              | X                  | X                 |
|                                                                     | Dapagliflozin                                               | R                                                             | R                  | X                                | X                              | X                  | X                 |
|                                                                     | Empagliflozin                                               | R                                                             | R                  | R                                | X                              | X                  | X                 |
| Direct oral anticoagulants for indications: VTE/atrial fibrillation | Ertugliflozin                                               | R                                                             | R                  | X                                | X                              | X                  | X                 |
|                                                                     | Apixaban                                                    | R/DA <sup>b</sup>                                             | R/DA <sup>b</sup>  | R/DA <sup>b</sup>                | R/DA <sup>b</sup>              | R/DA <sup>b</sup>  | C/DA <sup>b</sup> |
|                                                                     | Dabigatran                                                  | R/R                                                           | R/R                | R <sup>c</sup> /R <sup>c</sup>   | R <sup>c</sup> /R <sup>c</sup> | C/DA <sup>d</sup>  | C/C               |
|                                                                     | Edoxaban                                                    | R/X <sup>e</sup>                                              | R/R                | DA <sup>f</sup> /DA <sup>f</sup> | DA/DA                          | DA/DA              | X/X               |
| ARB/neprilysin inhibitor                                            | Rivaroxaban                                                 | R/R                                                           | R/R                | R/DA <sup>f</sup>                | R/DA                           | X/DA               | X/C               |
|                                                                     | Sacubitril/Valsartan                                        | R                                                             | R                  | R                                | R                              | DA <sup>g</sup>    | DA <sup>g</sup>   |
| Antiretrovirals                                                     | TDF                                                         | R                                                             | R                  | DA <sup>f</sup>                  | DA                             | DA                 | DA                |
|                                                                     | Emtricitabine                                               | R                                                             | R                  | DA <sup>f</sup>                  | DA                             | DA                 | DA                |
|                                                                     | Lamivudine                                                  | R                                                             | R                  | DA <sup>f</sup>                  | DA                             | DA                 | DA                |
|                                                                     | Elvitegravir/Cobicistat/Emtricitabine/TDF                   | R                                                             | R <sup>h</sup>     | X <sup>f</sup>                   | X                              | X                  | X                 |
|                                                                     | TDF/Emtricitabine <sup>i</sup>                              | R                                                             | R                  | X <sup>j</sup>                   | X <sup>j</sup>                 | X <sup>j</sup>     | X <sup>j</sup>    |
|                                                                     | Abacavir/Lamivudine                                         |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Efavirenz/Emtricitabine/TDF                                 |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Rilpivirine/Emtricitabine/TDF                               |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Dolutegravir/Abacavir/Lamivudine                            |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Tenofovir Alafenamide/Emtricitabine                         | R                                                             | R                  | R                                | R                              | X                  | X                 |
|                                                                     | Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Emtricitabine/Rilpivirine/Tenofovir Alafenamide             |                                                               |                    |                                  |                                |                    |                   |
| Direct-acting antihepacivirals                                      | Ledipasvir/Sofosbuvir                                       | R                                                             | R                  | R                                | R                              | C <sup>k</sup>     | C <sup>k</sup>    |
|                                                                     | Sofosbuvir/Velpatasvir                                      |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Sofosbuvir/Velpatasvir/Voxilaprevir                         |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Simeprevir                                                  |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Sofosbuvir                                                  |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Ombitasvir/Paritaprevir/Ritonavir                           | R                                                             | R                  | R                                | R                              | R                  | R                 |
|                                                                     | Elbasvir/Grazoprevir                                        |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Glecaprevir/Pibrentasvir                                    |                                                               |                    |                                  |                                |                    |                   |
|                                                                     | Daclatasvir                                                 |                                                               |                    |                                  |                                |                    |                   |

R, can be safely recommended at normal doses; DA, dose adjustment required for use; X, use not recommended; C, no manufacturer specific recommendation for use or dose adjustment, use with caution; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter 2; ARB, angiotensin receptor blocker; VTE, venous thromboembolism; TDF, tenofovir disoproxil fumarate; CrCl, creatinine clearance; P-gp, P-glycoprotein.

<sup>a</sup>Metformin should not be initiated in patients with an eGFR between 30 and 45 ml/min per 1.73 m<sup>2</sup>.

<sup>b</sup>Apixaban requires dose adjustment in atrial fibrillation if two of the following characteristics are met: serum creatinine  $\geq 1.5$  mg/dl, body weight  $\leq 60$  kg, age  $\geq 80$  years.

<sup>c</sup>Dabigatran requires dose adjustment in both VTE and atrial fibrillation for CrCl 30–50 ml/min with coadministration of P-gp inhibitors.

<sup>d</sup>Avoid dabigatran use in atrial fibrillation for CrCl  $< 30$  ml/min with coadministration of P-gp inhibitors.

<sup>e</sup>Avoid edoxaban use in atrial fibrillation for CrCl  $> 95$  ml/min because of increased risk of ischemic stroke.

<sup>f</sup>Requires no dose adjustment for CrCl 51–59 ml/min (edoxaban in VTE and atrial fibrillation, rivaroxaban in atrial fibrillation, ceftazidime/avibactam, ceftolozane/tazobactam, tenofovir disoproxil fumarate) or CrCl 50–59 ml/min (emtricitabine, lamivudine, elvitegravir/cobicistat/tenofovir disoproxil/emtricitabine) or eGFR 50–59 ml/min per 1.73 m<sup>2</sup> (meropenem/vaborbactam).

<sup>g</sup>Dose adjustment required for initial dose.

<sup>h</sup>Avoid initiating Elvitegravir/Cobicistat/Emtricitabine/TDF in CrCl  $< 70$  ml/min.

<sup>i</sup>Dose adjustment may be used for TDF/Emtricitabine in CrCl 30–49 ml/min.

<sup>j</sup>Use individual components. Dose adjustment for TDF and Emtricitabine for kidney function.

<sup>k</sup>No dose adjustments have been provided by the manufacturer in CrCl  $< 30$  ml/min.

**Table 3. Approach to medication assessment and deprescribing in CKD (8,9,11,77,79)**

| Step                       | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Assess kidney function  | Determine GFR to evaluate kidney function for drug dosing<br>Direct measurement of GFR may be necessary for dosing narrow therapeutic or toxic range drugs                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2. Medication history      | Collect complete medication list:<br>Include all prescription, over-the-counter and dietary supplements (including herbal, nonherbal, and vitamin supplements)<br>Collect history of drug allergies/sensitivities; adjustment or discontinuation of medication due to impaired kidney function or toxicity                                                                                                                                                                                                                                                                                                               |
| 3. Medication review       | Is the drug nephrotoxic or contraindicated in CKD or at a specific GFR level?<br>Is the drug or drug metabolite's half-life prolonged in CKD?<br>Is the risk of adverse effects or drug–drug interactions increased in CKD?<br>Does this drug have a narrow therapeutic or toxic range?                                                                                                                                                                                                                                                                                                                                  |
| 4. Adjust regimen          | Prescribing:<br>Calculate/adjust dose on the basis of Food and Drug Administration-approved product labeling, drug pharmacokinetic characteristics, and the patient's GFR<br>Refer to peer-reviewed literature recommendations if limited information in product labeling<br>Patients should consult with pharmacist or health professional before initiating over-the-counter medications or dietary supplements<br>Deprescribing:<br>Discuss rationale and plan with patient and care team<br>Deprescribe one medication at a time, consider agents with greatest harm and least benefit, consider patient preferences |
| 5. Drug therapy monitoring | Document and monitor for signs efficacy, toxicity, and change in symptoms with initiation or discontinuation of agent<br>Revise regimen on the basis of acute ( <i>e.g.</i> , intercurrent illness) or chronic changes/decline in patient's health status and/or kidney function                                                                                                                                                                                                                                                                                                                                         |

partly because of the paucity of data evaluating use with impaired kidney function. Exenatide and exenatide extended release should be avoided in patients with a creatinine clearance <30 ml/min because both are eliminated through the kidneys, whereas lixisenatide should not be used for patients with a creatinine clearance of <15 ml/min (70). Other agents, such as albiglutide, dulaglutide, and semaglutide, are not associated with kidney elimination and do not require a dose adjustment with impaired kidney function. Liraglutide is not eliminated through the kidneys but does carry a cautionary recommendation for use with any degree of kidney impairment (70,71). Liraglutide is also unique in this class because its use has been specifically evaluated in patients with CKD stage 3, revealing no negative effects on kidney function, and in patients with CKD stage 4, showing a slower progression of diabetic kidney disease (72,73). Finally, there have been post-marketing reports of both acute kidney failure and worsening of CKD in both patients with and without reduced kidney function for several agents in this class (70). The majority of these are in patients experiencing GI adverse effects, and the drug class carries a warning to monitor kidney function in patients with CKD who report severe GI symptoms.

The sodium-glucose cotransporter 2 inhibitors are oral agents for treatment of T2DM targeting kidney tubular glucose reabsorption. Efficacy of these agents can be affected by kidney function and specific dosing recommendations are summarized in Table 2 (74).

Finally, all available insulin preparations can be used in patients with CKD. However, because the kidney is responsible for 30%–80% of insulin removal, patients should be monitored for hypoglycemia due to decreased insulin elimination as kidney function declines (75). Insulin requirements should be tailored to meet individual needs, and no specific dose adjustment is recommended.

### Anticoagulant Agents in CKD

Many patients with CKD require anticoagulation for comorbid conditions and treatment with vitamin K antagonist or direct oral anticoagulants (DOACs). However, caution is warranted with DOAC use in CKD because these agents are partly eliminated by the kidneys (76). Unaltered dosing can result in an increased risk of bleeding. Although all DOACs can be used with impaired kidney function, the recommendations for dose adjustment are dependent on indication and kidney function. Of note, DOACs should be avoided in ESKD given the lack of data evaluating the efficacy and safety of these agents (76). Low molecular weight heparin should also be administered at a reduced dose with lower GFRs, and avoided in ESKD.

### Medication Reconciliation and Deprescribing in CKD

Several approaches have been proposed to address medication safety hazards in CKD (8,11,77). Much of the focus is on adherence to appropriate prescribing guidelines, medication reconciliation, evidence-based agent selection, dose modifications on the basis of altered kidney function and drug PK/PD, and monitoring of drug therapy response and kidney function (8,9,11). Special attention is also required for CKD drug dosing with many over-the-counter medications and dietary supplements (*i.e.*, herbal supplements, nonherbal supplements, and vitamins) (78). However, it is difficult to provide dosing and management recommendations for many herbals and vitamins with unknown toxicities.

The KDIGO guidelines provide a starting point for evaluating medication appropriateness for commonly used medications in CKD (Table 1). Since publication of the guidelines, a number of new agents used in management

of common comorbid conditions entered the market. Of these new agents, we have identified several drug classes and selected agents that may require dose adjustment or deprescription in CKD, detailed in Table 2. Decision-support platforms such as Micromedex and Lexicomp offer easily accessible monographs of prescription and over-the-counter medications to guide agent selection and dosing. The Natural Medicine Comprehensive Database is a useful resource to consider the safety of herbals, dietary supplements, vitamins, and other and nutraceuticals in CKD.

In addition to adherence to prescription guidelines, deprescribing is gaining attention for identifying and eliminating inappropriate medications. Deprescribing can be defined as “the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits.” (79) Studies involving deprescribing or drug therapy reviews in kidney disease have centered on the hemodialysis population, and deprescribing guidance for patients with predialysis CKD are lacking (80,81). Despite the paucity of guidelines for this population, health care providers can apply general principles of deprescribing in CKD (8,11,79).

A range of drug classes are candidates for deprescription in CKD. NSAIDs are priority for deprescribing in CKD because of potential adverse effects such as worsening of CKD, fluid retention, hyperkalemia, BP, and AKI (52,77,82). NSAIDs, including cyclooxygenase-2 inhibitors should be avoided in hypertension, CHF, and CKD of all causes (52). Other candidate drug classes for deprescribing in CKD include proton pump inhibitors, for which growing evidence indicates potential kidney and nonkidney-related harm with prolonged usage (83).

A general approach to medication assessment and deprescribing is proposed in Table 3. As outlined in the table, one should review the indication for each individual agent to determine whether the potential for harm outweighs the evidence for efficacy. For example, RAAS blockers, which can lead to hyperkalemia and AKI, should undergo a harm versus benefit evaluation, especially in patients where the benefits of treatment targets are unknown or equivocal.

Finally, given the complexity of medication management of the CKD population, there is strong justification for the involvement of an interprofessional team that includes pharmacists to prevent, identify, and resolve potential or actual medication-related problems (84,85). Although much of the evidence supporting pharmacist involvement in medication reconciliation and management is in the hemodialysis population, these best practices may also be extrapolated to the predialysis population.

## Summary

Medication management in CKD offers unique challenges, but presents providers with opportunities to enhance care quality to this high-risk population. Implementing strategies to evaluate the heavy medication burden of many patients with CKD, considering the risks and benefits of all prescribed agents, and deprescribing when indicated may improve patient outcomes. The implications of reduced kidney function in a disease population with a range of comorbidities are substantial, and recognizing these can have a significant effect on care management of patients with CKD, and has the potential to reduce much of their morbidity and mortality.

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