Chapter 62: Chronic Kidney Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 76, Chronic Kidney Disease.

KEY CONCEPTS

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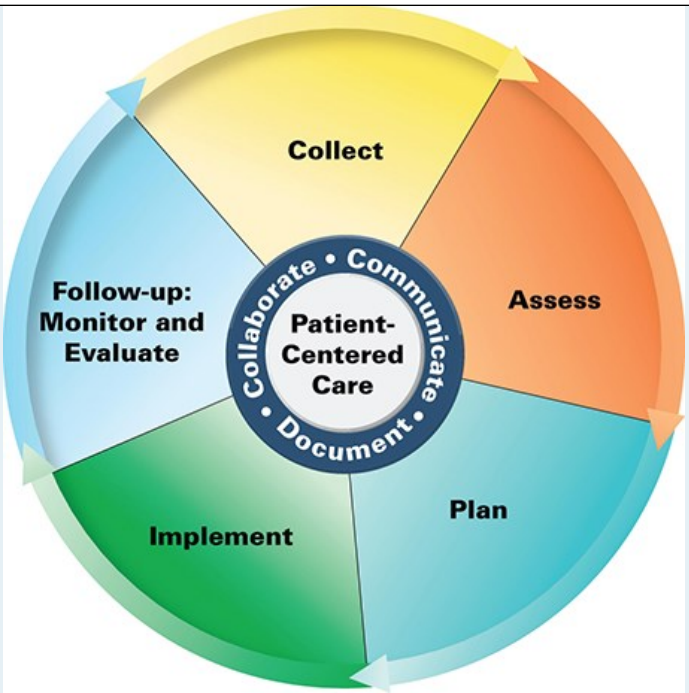
1. Chronic kidney disease (CKD) is classified based on the cause of kidney disease, assessment of glomerular filtration rate, and extent of albuminuria over at least a 3-month period.
2. Guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) provide information to assist healthcare providers in clinical decision making and the design of appropriate therapy to manage CKD progression and the associated complications.
3. Patient education and shared decision making play a critical role in the appropriate management of patients with CKD. Studies of multidisciplinary teams in CKD clinics have demonstrated significant benefits in slowing progression of CKD and reduced mortality.
4. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are primary pharmacologic treatments to delay progression of CKD in patients with category A2-A3 albuminuria because of their effects on renal hemodynamics to reduce intraglomerular pressure and albuminuria.
5. Sodium Glucose Transport-2 inhibitors (SGLT2i) have emerged as the latest treatment to prevent progression to later stages of CKD and ESRD in patients with Type 2 diabetes and other kidney diseases associated with albuminuria.

PATIENT CARE PROCESS

Patient Care Process for Chronic Kidney Disease (CKD)



Collect

- Patient characteristics (eg, age, CKD stage [see Fig. 62-1] and cause of CKD, medication allergies)
- Past medical history
- Social history (eg, smoking), family/friend supports
- Current medications including OTC (eg, NSAID use), herbals, dietary supplements
- Objective data:
  - Blood pressure, heart rate, weight
  - Labs as outlined in Table 62-4

Assess

- Serum creatinine, glomerular filtration rate (GFR), or creatinine clearance
- Presence of albuminuria (see Fig. 62-1)
- Serum potassium concentration—assess frequently in patients with CKD and heart failure requiring adjustment of diuretics and/or ACEI
- Blood pressure (see targets in Fig. 62-3)—consider use of home blood pressure monitor
- Insurance coverage of medications, current out of pocket cost of medications
- Medication adherence
- Potential drug interactions
- Need for renal dose adjustments
- Other recommendations as outlined in Table 62-2 (eg, vaccines, lifestyle modifications)

Plan

- Drug therapy recommendations, including dose, route, frequency, and duration
- Monitoring parameters, including frequency and timing of follow-up
- Patient education, including purpose of new or changed treatment, medication side effects, medication administration
- Self-monitoring for resolution of symptoms and blood pressure targets, medication to hold on sick days if vomiting or diarrhea occur (eg, ACEI/ARB; SGLT2 inhibitors)
- Referrals to other providers when appropriate (eg, dietitian, occupational therapist, social worker, endocrinologist, CKD clinic)

Implement*

- Provide patient education on all elements of the treatment plan
- Use motivational interviewing strategies to maximize adherence
- Schedule follow-up labs, adherence assessment

Follow-up: Monitor and Evaluate

- Resolution of CKD symptoms
- Presence of adverse effects (eg, dizziness, hypoglycemia)
- Patient adherence to treatment plan using multiple sources of information

****Communicate with patient, caregivers, and CKD multidisciplinary team.***

BEYOND THE BOOK

BEYOND THE BOOK

Visit The Kidney Failure Risk Equation Website (available at https://kidneyfailurerisk.com/). Watch the video then practice using the Kidney Failure Risk Equation to calculate the 2-year and 5-year probability of treated kidney failure (dialysis or transplantation) for a potential patient with CKD Stage G3 to G5. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

1 Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function, present for 3 months or longer. Lower glomerular filtration rate (GFR) and a higher urinary albumin to creatinine ratio (ACR) are both independently associated with adverse events.[1] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of CKD classification system stages kidney disease by cause, GFR, and albuminuria. Figure 62-1 shows the KDIGO GFR and albuminuria categories along with the prognosis based on these factors.

FIGURE 62-1

KDIGO GFR and albuminuria categories and prognosis of CKD by category. To meet criteria for CKD there must be a significant reduction in GFR (categories 3a-5) or there must also be evidence of kidney damage (categories 1 and 2) for 3 months or greater. Prognosis Scale—Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. (CKD, chronic kidney disease; GFR,

glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.)

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (mL/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The prognosis of CKD is dependent on the following factors: (a) cause of kidney disease; (b) GFR at time of diagnosis; (c) degree of albuminuria measured by ACR; and (d) presence of other comorbid conditions. Patients with any of the following should be referred to a nephrologist for evaluation and collaborative management: persistent and significant albuminuria (ACR >100 mg/g [>11.3 mg/mmol]), progression of CKD (eg, a marked but nonacute decline in GFR), presence of a non-surgical cause of hematuria, hypertension refractory to treatment (eg, ≥4 antihypertensive agents), persistent abnormalities of serum potassium, recurrent or extensive nephrolithiasis, GFR less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), or hereditary kidney disease such as polycystic kidney disease even in the presence of normal GFR and ACR.[1]

CKD is often unrecognized and this contributes to significant morbidity, premature mortality, and a poorer prognosis when it is finally diagnosed. This chapter primarily covers the epidemiology, etiology, pathophysiology, clinical presentation, and treatment of progressive CKD. The reader is referred to Chapter 63 for a detailed discussion of management and monitoring strategies for secondary complications of CKD.

EPIDEMIOLOGY

CKD is recognized as a significant global public health problem.[2] People with CKD experience high morbidity and mortality rates with a resulting economic burden to healthcare systems due to frequent hospitalizations and the high cost of chronic dialysis and kidney transplantation. CKD affects more than 697 million individuals worldwide. In 2017, 1.2 million deaths and 35.8 million disability-adjusted life years were attributed to CKD. As a result, many countries have implemented public health initiatives to reduce the proportion of the population with CKD; increase CKD patient awareness through targeted screening programs; reduce the rate of new cases of CKD G5; and reduce mortality in persons with CKD.[2]

Diabetic kidney disease is the most frequent cause of end-stage (G5) kidney failure worldwide. Approximately 25% to 50% of all patients receiving dialysis have diabetic kidney disease.[3] In first-world countries, the leading cause of CKD is diabetes mellitus followed by hypertension.[4] It is projected that the aging population and other changes in the demographics will result in an increased incidence and subsequent increase in prevalence of Stage 5 CKD by 2030.[5] The prevalence of CKD increases with age, with the highest prevalence in individuals over 60 years mainly attributed to a decrease in estimated GFR (eGFR, less than 60 mL/min/1.73 m^2).[6] While there is some debate as to whether the eGFR decline in older individuals as a consequence of the normal physiological aging process should be considered a *disease* necessitating the label of CKD, the fact remains that patients with reduced eGFR and albuminuria suffer from worse health outcomes regardless of age.[1]

Specific racial, social, and environmental factors are important to consider when evaluating risk of progressive CKD in individual patients. Racial health disparities in CKD also exist and contribute to differing CKD rates. There is evidence for higher risk of CKD progression in patients of African, Hispanic, and Asian (South, East, and Pacific Islanders) descent and Indigenous people compared to Caucasians. This is partly explained by biological factors

(eg, blood pressure) and comorbidities such as diabetes, and cardiovascular disease. However, despite a higher risk of CKD progression, there is a lower risk of mortality for patients of Asian and Hispanic descent compared to Caucasians, and a key gap in the literature is understanding why they live longer despite having a higher prevalence of comorbidities such as diabetes, cardiovascular disease, and heart failure.[7] Increased risk of CKD in high-risk ethnic groups may be tackled through closer monitoring and management of renal comorbidities such as diabetes and cardiovascular disease, for example, through albuminuria and blood pressure measurement.[7]

With regards to socioeconomic factors, the likelihood of CKD is higher in individuals with lower income and education.[8] Multiple studies conducted in the United States, Canada, and Europe have shown a strong association between low-socioeconomic status and higher incidence, prevalence and more complications related to CKD. Poverty is known to affect some of the most important social determinants of health, such as developing healthy habits, getting healthcare in a timely manner and environmental exposure to nephrotoxic agents such as lead, cadmium, and arsenic. A higher prevalence of births with low-birth weight promotes not only less development in terms of renal mass but also an increased risk of hypertension and CKD. Depression, anxiety, and increased exposure to addictions also promote the activation of the sympathetic nervous system and an increased release of cytokines that can influence the pathogenesis of kidney damage. An increased intake of sodium, sweetened beverages, and foods with phosphorus has also been reported, and the chances of receiving proper treatment to slow the progression of kidney damage are lower. A clearer understanding of the situations of vulnerable populations could allow for better public health measures to reduce the burden of kidney disease.[9]

ETIOLOGY

Susceptibility and Initiation Risk Factors

Clinical and sociodemographic risk factors for susceptibility to and initiation of CKD are listed in Table 62-1 and are useful for identifying individuals at high risk of developing CKD.[10]

TABLE 62-1

Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease

Clinical Factors
Diabetes
Hypertension
Obesity
Smoking
Autoimmune diseases, such as lupus, rheumatoid arthritis, connective tissue disease, vasculitis
Systemic infections, such as group A *streptococcus* causing post-infectious glomerulonephritis (PIGN)
Artherosclerotic vascular disease
Urinary tract infections, such as recurrent pyelonephritis
Lower urinary tract obstruction from prostatic hypertrophy, neurogenic bladder, kidney stones
Neoplasia, such as multiple myeloma, renal cell carcinoma
First degree relative with CKD
History of acute kidney injury (AKI) including recurrent episodes of dehydration
Reduction in kidney mass, such as congenital single kidney, post nephrectomy, scarring from reflux nephropathy
Exposure to nephrotoxic drugs, such as chronic use acetaminophen, NSAIDs, COX-2 inhibitors, lithium, cyclosporine, tacrolimus, contrast dyes, certain chemotherapy drugs, etc.
Pregnancy complications including edema, hypertension, proteinuria
Low-birth weight
Chronic viral infections, such as Hepatitis B and C, HIV
Hereditary polycystic kidney disease
Sociodemographic Factors
Older age
Ethnic minority status
Exposure to certain chemical and environmental conditions
Low income/education

Data from References 1,10.

Predicting Risk of Progression

KIDGO recommends that all patients with CKD be staged according to eGFR and ACR and that their prognosis be considered to help guide further testing and treatment decisions (Fig. 62-1). Estimating equations such as the kidney failure risk equation (KFRE), which incorporates urine data, sex, age, and GFR, have also been used and provide an accurate 2- and 5-year risk of progression to kidney failure for individuals with stage 3 to 5 CKD.[11] The KFRE has been widely validated in multiple international cohorts and pediatric populations and provides the best current evidence-based approach to point-of-care risk of progression to be used in combination with expert clinical judgment.[12] Risk equations may also be beneficial to help align resources with risk in assigning priority for referral to nephrologists.

Progression Risk Factors

Progression risk factors are those associated with further decline in kidney function. Persistence of the underlying initiation factors (eg, diabetes mellitus, hypertension) is the most important predictor of progressive CKD.

Diabetes mellitus

Type 2 diabetes accounts for about 90% of the 460 million people with diabetes in the world. About half of these patients will develop kidney disease.[3] The KDIGO Clinical Practice Guideline for Diabetes Management in CKD recommends an individualized hemoglobin A_{1C} (HbA1c) target ranging from <6.5% (0.065; 48 mmol/mol) to <8.0% (0.08; 64 mmol/mol) in patients with diabetes and CKD[13] (Evidence level 1C). Achieving HbA1c targets prevents the surrogate endpoints of microalbuminuria and macroalbuminuria associated with diabetic chronic kidney disease (DIABETIC CKD).

Hypertension

The 2021 KDIGO guideline for the management of blood pressure in CKD recommends control blood pressure at all categories of CKD regardless of the underlying cause since early treatment of hypertension and achievement of target blood pressure have been demonstrated to slow the rate of progression of CKD.[14]

Albuminuria

Albuminuria is a strong independent predictor of accelerated progression of CKD and also a risk factor for CV mortality and morbidity.[1] Albuminuria remains the primary modifiable risk factor associated with CKD progression in most patients.

Smoking

Smoking is associated with kidney damage in the general population as well as in patients with diabetes and hypertension.[15] Acute reductions in GFR and an increase in urinary albumin excretion, heart rate, and blood pressure, likely secondary to nicotine exposure, have been reported.[16] Smoking is also associated with an increase in CV events in people with CKD.[1]

Obesity

Population data have demonstrated an increased risk of CKD G5 in overweight and obese subjects.[17] The risk of CKD 5 was directly related to the magnitude of obesity and remained even after adjustment for diabetes and hypertension. A body mass index (BMI) greater than or equal to 25 kg/m^2 at the age of 20 years has been associated with a threefold increase in risk of CKD compared with a BMI lower than 25 kg/m^2.[18] This association has also been shown in healthy young and middle-aged individuals without CKD or albuminuria.[19] Intentional weight loss in individuals with CKD was associated with decreases in albuminuria, systolic blood pressure, and stabilization in GFR.[20] These data suggest that weight reduction be included as part of the treatment of CKD (Table 62-2).

TABLE 62-2

Recommendations for Individuals with Chronic Kidney Disease

Nonpharmacologic
Exercise 30 minutes five times per week [1D]
Weight loss if BMI >25 kg/m^2 [1D]
Smoking cessation [1D]
Alcohol: Two standard drinks per day for men and one standard drink per day for women[a] [2D]
If hypertension: Low-sodium diet (<2 g/day, <90 mmol/day) [1C]
Pharmacologic
Adjust medication doses for kidney function [1A]
Seek pharmacist or medical advice before using over-the-counter medicines or nutritional protein supplements [1B]
Herbal medicines are not recommended [1B]
Temporarily discontinue potentially nephrotoxic/renally excreted drugs if eGFR <60 mL/min/1.73 m^2 in patients who are acutely unwell or hypovolemic (eg, metformin, RAAS blockers, diuretics, NSAIDs/COX II inhibitors, lithium, digoxin) [1C]
Vaccines
Influenza yearly [1B]
Pneumococcal vaccine if eGFR <30 mL/min/1.73 m^2, nephrotic syndrome, diabetes, or receiving immunosuppression. Single booster dose at year 5 [1B]
Hepatitis B vaccine if eGFR <30 mL/min/1.73 m^2 and risk of progression of CKD [1B]
ASA suggested for patients at risk for atherosclerotic events unless there is an increased bleeding risk [2B]
Avoid oral phosphate-containing bowel preparations in people with a GFR <60 mL/min/1.73 m^2 (0.58 mL/s/m^2) or in those known to be at risk of phosphate nephropathy [1A]

BMI, body mass index; CKD, chronic kidney disease; COX, cyclooxygenase; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system.

See Table 62-3 for definitions of evidence grading in brackets.

[a]Standard drink: 30 mL spirits, 100 mL wine, 285 mL full-strength beer, and 425 mL light beer.

Data from References 1 and 13.

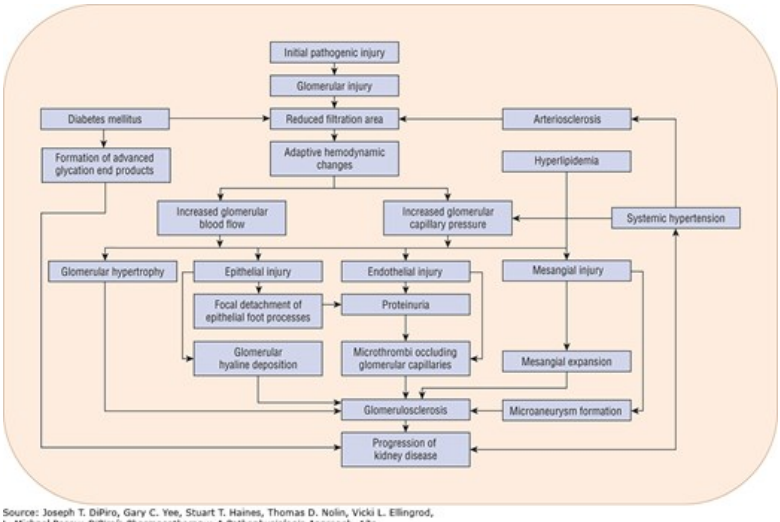
PATHOPHYSIOLOGY

Chronic Kidney Disease

Progression of CKD to more advanced stages (G4-G5) typically occurs over decades in the majority of people, with the precise mechanism of kidney damage dependent on the etiology of the disease and strongly associated with age, sex, and urine ACR. As evidenced by the variety of initiation and progression factors, kidney damage can result from an array of heterogeneous causes. Diabetic CKD is characterized by glomerular mesangial expansion while with hypertensive nephrosclerosis, the kidney's arterioles have arteriolar hyalinosis. Polycystic kidney disease is characterized by the development and expansion of renal cysts. While the initial structural damage depends on the primary disease affecting the kidney, the key elements of the pathway to ESRD are (a) loss of nephron mass, (b) glomerular capillary hypertension, and (c) albuminuria (Fig. 62-2).

FIGURE 62-2

Proposed mechanisms of progression of kidney disease.



Exposure to any of the initiation risk factors can result in loss of nephron mass. In response to the decrease in nephron function, the remaining nephrons compensate through the process of autoregulation. With nephron loss and the resulting reduction in perfusion pressure and GFR, renin release from the juxtaglomerular apparatus increases and converts angiotensinogen to angiotensin I, which is then converted to angiotensin II (ATII). ATII is a potent vasoconstrictor of both afferent and efferent arterioles, but it preferentially affects the efferent arterioles, leading to increased pressure within the glomerular capillaries and consequent increased filtration fraction. Initially, this compensatory action may be adaptive and beneficial; however, over time it can lead to the development of intraglomerular hypertension and hypertrophy and a further decline in the number of functioning nephrons. High intraglomerular capillary pressure impairs the size-selective function of the glomerular permeability barrier, resulting in increased urinary excretion of albumin and albuminuria. The development of intraglomerular hypertension usually parallels the development of systemic hypertension. ATII as well as aldosterone may also mediate CKD progression through nonhemodynamic effects by increasing growth factors (eg, transforming growth factor beta [TGF-β]) and causing cellular proliferation and hypertrophy of the glomerular endothelial cells, epithelial cells, and fibroblasts ultimately resulting in further inflammation and fibrosis.[21]

Proteinuria alone may promote progressive loss of nephrons as a result of direct cellular damage. Filtered proteins such as albumin, transferrin, complement factors, immunoglobulins, cytokines, and ATII are toxic to kidney tubular cells. Studies have demonstrated that the presence of these proteins in the renal tubule leads to increased production of inflammatory and vasoactive cytokines such as endothelin and monocyte chemoattractant protein-1 (MCP-1).[22] Proteinuria is also associated with the activation of complement components on the apical membrane of proximal tubules. Intratubular complement activation may be the key mechanism of damage in the progressive proteinuric nephropathies.[22] Furthermore, these events ultimately lead to scarring of the interstitium, progressive loss of structural nephron units, and a reduction in GFR.

CLINICAL PRESENTATION

CKD is often asymptomatic, which is a reason many patients are not diagnosed with the disease until they reach CKD G4-G5 and may be near the point of requiring renal replacement therapy such as dialysis or kidney transplantation. This problem has prompted automated reporting by clinical laboratories of the eGFR as determined by the estimating equations [Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI equation)] for the purpose of identifying individuals with CKD earlier (see Chapter e60). Comprehensive screening for CKD includes analysis of eGFR and ACR (Fig. 62-1) and risk stratification for progression using the Kidney Failure Risk Equation. Clinicians must understand how to interpret the eGFR and values for urine albumin excretion to appropriately stage individuals with CKD. Chapter e60 provides a detailed discussion of the methods available for detection of urinary albumin and protein.

CLINICAL PRESENTATION: CKD Stages G1-G5

Symptoms (usually not observed until Stage G4-G5)

- Fatigue, weakness, shortness of breath, mental confusion, nausea and vomiting, and loss of appetite, itching, cold intolerance, and peripheral neuropathies are common

Signs

- Edema, weight gain (from accumulation of fluid), changes in urine output (volume and consistency), "foaming" of urine (indicative of albuminuria), elevated blood pressure (hypertension is a common cause and result of CKD)

Laboratory Tests

- *Decreased*: eGFR, bicarbonate (metabolic acidosis), Hb/hematocrit (Hct) (anemia), transferrin saturation (TSat) and/or ferritin (iron deficiency; note: ferritin may be increased due to inflammatory conditions), vitamin D levels, albumin (malnutrition)
- *Increased*: Serum creatinine, blood urea nitrogen, potassium, phosphorus, PTH, ACR, glucose/HbA1c (diabetes is a cause of CKD), low-density lipoprotein (LDL), and triglycerides

Other Diagnostic Tests

- Urine sediment abnormalities (hematuria, red blood cell and white blood cell casts, renal tubular epithelial cells)
- Pathologic abnormalities indicating glomerular, vascular, tubulointerstitial disease, or cystic and congenital diseases
- Structural abnormalities such as polycystic kidneys, renal masses, renal artery stenosis, cortical scarring due to infarcts and pyelonephritis, or small kidneys (common in more severe CKD) detected by imaging studies (eg, ultrasound, computed tomography, magnetic resonance imaging, angiography)

TREATMENT

Desired Outcome

The overall goal of treatment is to delay or prevent progression of CKD.

General Approach to Treatment

Individuals with CKD should be evaluated frequently to assess the risk of progression of CKD, to identify the presence and causes of secondary complications and comorbid conditions, and to receive treatment for these complications prior to development of Stage G5 CKD. Many nonpharmacologic and pharmacologic recommendations can be broadly applied as part of the general approach to care for all CKD patients (Table 62-2).

Management of CKD should be based on the KDIGO consensus guidelines (available at www.kdigo.org) which are based on evidence and expert recommendations. The available KDIGO clinical practice guidelines relevant to CKD address evaluation and management of CKD, blood pressure, diabetes, glomerulonephritis, lipid management, and hepatitis C in CKD. Table 62-3 provides a guide to the grading and strength of recommendations used in these guidelines.

TABLE 62-3

KDIGO Guidelines: Grading and Strength of Recommendations

Grade	Description	Implications for Clinicians
Level 1	"We recommend"	Most patients should receive the recommended course of action.
Level 2	"We suggest"	Different choices will be appropriate for different patients. Each patient needs help arrive at a management decision consistent with her or his values and preferences.
Grade	**Quality of Evidence**	**Meaning**
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

The strength of recommendation is indicated as Level 1, Level 2, or Not Graded. The quality of the supporting evidence is shown as A, B, C, or D.

Data from Reference 1.

Appropriate management of CKD ideally involves a multidisciplinary approach to address the nonpharmacologic and pharmacologic interventions, dietary education, and social/financial concerns. Multidisciplinary CKD team models that have included members such as a nephrologist, nurse, dietitian, pharmacist, and social worker have demonstrated significant slowing of CKD progression, longer time to start of renal replacement therapy (dialysis or kidney transplant), and reduction in all-cause mortality.[23] Estimates in the pediatric CKD population indicate that the additional salary costs of the multidisciplinary team (pharmacist, nurse, social worker, dietician, data manager) could be recovered in 1 year if dialysis was delayed by 1 year in only 2% of patients.[24]

Drug-dosing guidelines based on the degree of kidney function should be followed, and a complete medication history of prescription and nonprescription medications, as well as herbals and nutritional supplements, should be obtained and routinely updated. Appropriate measures should also be taken for patients with CKD to decrease the risk of nephrotoxicity from radiocontrast agents, antibiotics such as aminoglycosides, as well as from nonsteroidal anti-inflammatory drugs and ACEIs (Chapter 65).[25]

Nonpharmacologic Therapy

Nonpharmacologic therapies for CKD include diet and lifestyle interventions targeted at reducing the risk for CKD progression and are outlined in Table 62-2.

Pharmacologic Therapy

Pharmacologic therapies used to slow CKD progression include drugs with demonstrated benefits to reduce albuminuria and to manage the causal factors for CKD primarily hypertension and diabetes. The next sections focus on pharmacologic therapy targeting these factors. Glomerular disease is the third leading cause of CKD and a review of the treatment strategies for glomerulonephritis is provided in Chapter e66.

Albuminuria

ACEIs and ARBs

4 Evidence from clinical trials has confirmed the beneficial effects of ACEIs and ARBs on kidney function for patients with albuminuria. A meta-analysis has shown that the effects of ACEIs or ARBs on key CKD outcomes such as doubling of serum creatinine and prevention of progression of micro- to macroalbuminuria are equivalent and, thus, they can be used interchangeably.[26] An ACEI or an ARB should be used as first-line therapy if the patient urine albumin excretion is in category A2 or greater (ACR >30 mg/g (>3.4 mg/mmol)) (see Fig. 62-3 and Table 62-4). The antiproteinuric effect of ACEIs and ARBs is a class effect and not specific to any one agent.[26] For patients with hypertension, the primary goal is to achieve the target blood pressure while a secondary goal is to control albuminuria. Specific dosing recommendations for ACEIs and ARBs for the treatment of albuminuria have not been established; consequently, the lowest recommended dose should be initiated and titrated up to the maximally tolerated dose. The dose is usually increased until albuminuria is reduced by 30% to 50% or side effects such as a greater than 30% increase in serum creatinine (Scr) concentration or elevation in serum potassium occur or the maximum dose for hypertension is achieved (see Table 62-5). When these drugs are used in patients with eGFR <30 mL/min per 1.73 m^2, close monitoring of serum potassium level is required. However, in patients with CKD G5 who are experiencing uremic symptoms or very high serum potassium levels (eg, K ≥ 6 mEq/L [mmol/L]), it is reasonable to discontinue ACEI or ARB treatment temporarily with the aim of increasing eGFR to hold off starting renal replacement therapy. The STOP-ACEi Trial is testing the hypothesis that stopping treatment with ACEi, or ARB compared with continuing these treatments, improves or stabilizes renal function in patients with G4 or G5 CKD.[27] If patients exhibit a cough with an ACEI, a switch to an ARB is appropriate. Advise contraception in women of childbearing age who are receiving ACEI or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant as these drugs can impair fetal kidney function especially with exposure during the second and third trimester.[13] Patients should be counseled to hold ACEI or ARB on sick days (ie, vomiting or diarrhea). A thorough discussion of dose, dose titration, monitoring, and adverse effects of ACEIs and ARBs is presented in Chapter 30.

FIGURE 62-3

Treatment of hypertension in chronic kidney disease. (ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; CV, cardiovascular.)

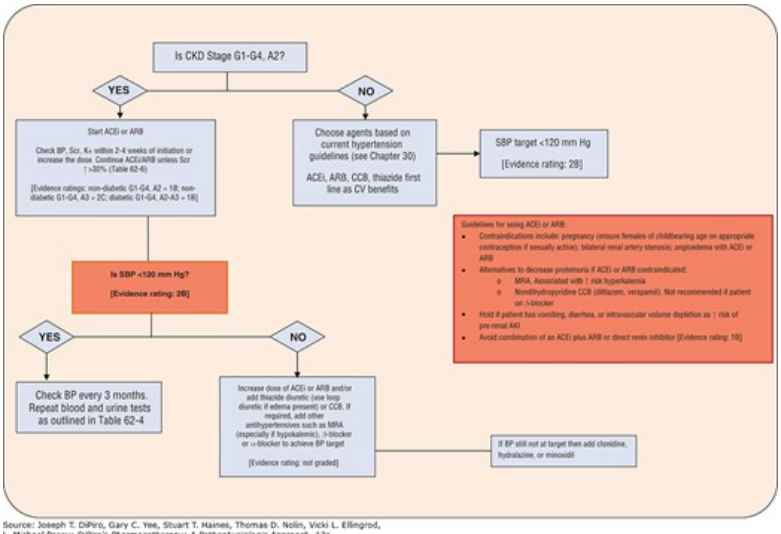


TABLE 62-4

Recommended Monitoring Intervals for Outcome Measure in Patients with Chronic Kidney Disease (Evidence Rating: Not Graded)

		Albuminuria Stage (based on ACR in mg/g)		
KDIGO GFR Category	**eGFR (mL/min/1.73 m^2)**	**A1: <30 mg/g (3 mg/mmol)**	**A2: 30-300 mg/g (3-30 mg/mmol)**	**A3: >300 mg/g (30 mg/mmol)**
1	≥90	12 months	12 months	6 months
2	60-89	12 months	12 months	6 months
3a	45-59	12 months	6 months	4 months
3b	30-44	6 months	4 months	4 months
4	15-29	4 months	4 months	2-3 months
5	<15	1-3 months	1-3 months	1-3 months

Blood tests to monitor: CBC, Na, K, Cl, bicarbonate, urea, creatinine, and eGFR. If DKD, add HbA1c. Fasting lipid profile at least yearly. At CKD category 3b or later: also add albumin, calcium, phosphorus, parathyroid hormone, serum iron, TIBC, and ferritin.

Urine tests to monitor: uACR (or uPCR if indicated), standard urinalysis, and urine culture and sensitivity only if symptoms suggestive of urinary tract infection.

Data from Reference 1.

TABLE 62-5

Guidelines for Monitoring Serum Creatinine and Potassium During ACEI or ARB Treatment

Adverse Drug Reaction	Monitoring Parameter	Therapeutic Adjustments	Review
↑ Scr	Scr to calculate eGFR If eGFR ≥60 mL/min/1.73 m^2, repeat in 4-12 weeks If eGFR 30-59 mL/min/1.73 m^2, repeat in 2-4 weeks If eGFR < 30 mL/min/1.73 m^2, repeat in ≤2weeks	• Scr ↑0%-15%, no dose change • Scr ↑15%-30%, no dose change but repeat Scr in 2 weeks to ensure it is stable • Scr ↑31%-50%, reduce dose and repeat Scr every 1-2 weeks until Scr within 30% of baseline • Scr ↑>50%, discontinue ACE or ARB and repeat Scr every 1-2 weeks until Scr is within 15% of baseline value	If Scr ↑>30%, review for: • Causes of AKI • Hold ACEI/ARB if vomiting, diarrhea, or volume depletion • Reassess any contributing meds (eg, diuretics, NSAIDs, COX 2 inhibitors) • Consider renal artery stenosis If Scr ↑<30%, increase dose of ACEI/ARB to maximally tolerated dose
Hyperkalemia	Serum K+ at same intervals as eGFR above	If K+>5 mEq/L (mmol/L), advise dietary K+ restriction If K+>6 mEq/L (mmol/L), consider treatment with diuretics that can lower K+ (eg, thiazide, loop) if appropriate; sodium bicarbonate tablets for patients with acidosis; potassium binders. If unable to lower K+ to <5.5 mEq/L (mmol/L), decrease or stop ACEI/ARB	• Concurrent drugs which may cause hyperkalemia (eg, MRAs, potassium supplements) • Dietary potassium intake review preferable by a dietitian

Data from Reference 13.

The lack of response of some patients to ACEI or ARB therapy may be due to aldosterone escape from renin–angiotensin–aldosterone system (RAAS) blockade. Combination therapy with an ACEI plus an ARB or direct renin inhibitor (eg, aliskiren) produces a more complete blockade of the RAAS and results in a greater reduction in macroalbuminuria.[28] However, several trials have failed to show that dual blockade of the RAAS either slowed progression of CKD or decreased CV events.[29-32] Combination therapy in these trials was also associated with increased risks of hyperkalemia and AKI. Thus, the combination of an ACEI plus an ARB or aliskiren for the treatment of albuminuria is to be avoided (Evidence level 1B).[14]

Sodium Glucose Transport-2 Inhibitors

4 Sodium glucose transport-2 inhibitors (SGLT2i) slow progression of both Type 2 diabetic and nondiabetic proteinuric CKD with benefits that are

independent of the glucose lowering effect.[33] By reducing glucose and sodium reabsorption in the proximal tubule of the kidney, these agents decrease glomerular hyperfiltration and reduce glomerular hypertension. Recent trials have demonstrated the benefits of these agents (Table 62-6). These trials have shown that SGLT2i significantly slow progression of kidney disease, reduce the need for dialysis or transplantation, and decrease mortality.[33,34] The slowing of progression of CKD equates to a gain of 15.1 years before the average CREDENCE trial patient (age 63 years; eGFR = 56 mL/min/1.83 m^2; receiving an ACEI/ARB) would reach an eGFR = 10 mL/min/1.73 m^2.[34] Hence, SGLT2i could significantly reduce the need for dialysis or kidney transplant in many patients with diabetic CKD and are an exciting advance in treatment for clinicians. SGLT2i should be considered after ACEI/ARB in all patients with diabetic CKD due to Type 2 diabetes who have an eGFR ≥20 mL/min/1.73 m^2 and ACR >200 mg/g (22.6 mg/mmol). Once started, SGLT2i should be continued until dialysis or kidney transplantation. These agents are not used in patients with CKD from Type 1 diabetes due to a significantly higher risk of diabetic ketoacidosis (DKA).[35] SGLT2i may cause euglycemic DKA which is rare, affecting approximately one in 1,000 patients based on real world data with 40% of cases occurring during a hospital stay. Blood glucose is typically less than 252 mg/dL (14 mmol/L) (range 216-324 mg/dL [12-18 mmol/L]). There is a higher risk for euglycemic DKA in Type 2 diabetics who are receiving insulin. Most patients will present with DKA within 2 months of starting a SGLT2i with some cases occurring shortly after SGLT2i discontinuation. Most patients with SGLT2i induced DKA will have a precipitating event such as dehydration, infection, surgery, and changes in insulin dose being commonly reported.[36] Symptoms of DKA associated with SGLT2i use are similar to DKA in general, with nausea, vomiting, and abdominal pain most commonly reported. However, these patients may not present with symptoms of dehydration to the same degree as other DKA patients due to the lack of hyperglycemia.[37]

TABLE 62-6

SGLT2 Inhibitor and MRA CKD Trials

Study	CREDENCE	Dapa-CKD	FIDELIO-DKD
Populations			
Age (mean ±SD)	63±9.2	61.9±12.1	65.6±9.1
CKD inclusion criteria	ACR >300-5,000 mg/g + eGFR 30-<90 mL/min/1.73 m^2; Type 2 DM	eGFR 25-75 mL/min/1.73 m^2; ACR 200-5,000 mg/g (22.6-566 mg/mmol); Type 2 DM & nondiabetics included	ACR 30-<300 mg/g (3.4-34 mg/mmol) + eGFR 25-<60 mL/min/1.73 m^2 OR ACR 300-5,000 mg/g (34-566 mg/mmol) + eGFR 25-<75 mL/min/1.73 m^2; Type 2 DM
Race distribution	White 66.6%; Asian 19.9%; Black 5.15%	White 53.2%; Asian 34.1%; Black 4.4%	White 63.3%; Asian 25.4%; Black 4.7%
Mean eGFR	56.2±18.2	43.1±12.4	44.3±12.6
Median UACR (IQR)	927 (463-1833 mg/g) or 105 (52-207 mg/mmol)	965 (472-1,903 mg/g) or 109 (53-215 mg/mmol)	852 (446-1,634 mg/g) or 96 (50-185 mg/mmol)
Baseline medications	ACEi or ARB; no MRAs or DRIs	ACEI or ARB	ACEI or ARB
Study medication	Canagliflozin 100 mg daily	Dapagliflozin 10 mg daily	Finerenone 10 mg daily if eGFR <60 mL/min/1.73 m^2, increased to 20 mg daily if tolerated OR 20 mg daily if eGFR >60

			mL/min/1.73 m^2
Results			
Number of participants	4,401	4,304	5,674
Primary outcome	Occurrence of: ESKD (established dialysis, transplant or eGFR persistently <15 mL/min/1.73 m^2) + doubling of baseline creatinine + death from renal or CV cause (HR 0.7 [0.59-0.82]	Time to event of: ESKD (established dialysis, transplant or eGFR persistently <15 mL/min/1.73 m^2) + decline in eGFR by at least 50% + death from renal or CV cause (HR 0.61 [0.51-0.72]	Time to event of: ESKD (established dialysis, transplant or eGFR persistently <15 mL/min/1.73 m^2) + decline in eGFR by 40% from baseline + death from renal (HR 0.82 [0.73-0.93]
NNT to prevent primary outcome	22 (15-38) patients over 2.5 years	19 (14-29) patients over 3 years	29 (16-166) patients over 3 years
Key secondary outcome	CV death + hospitalization for HF (HR 0.69 [0.57-0.83]	Composite kidney outcome (50% decline, ESKD or renal death); composite CV outcome; death from any cause (HR 0.56, 0.71, 0.69, respectively)	CV death + hospitalization for HR + nonfatal MI + nonfatal stroke (HR 0.86 [0.75-0.99])
Adverse effects	Genital mycotic infections, euglycemic DKA (rare)	Genital mycotic infections, euglycemic DKA (rare)	Hyperkalemia

CREDENCE, Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy; Dapa-CKD, Dapagliflozin in Patients with Chronic Kidney Disease; FIDELIO-DKD, Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes.

Data from References 33,34,38.

Patients at increased risk of volume depletion, mycotic genital infections (eg, vaginal yeast infections, Fournier's gangrene), women with a history of urinary tract infections, those with indwelling foley catheters may not be good candidates for this class of medications. Genital mycotic infections occur in approximately one in three patients and may be treated with topical or oral antifungals with no need to discontinue the SGLT2i.[39] The exception to this is Fournier's gangrene which requires incision and drainage and IV antibiotics. Patients should seek urgent medical care if pain, tenderness, erythema, swelling in genital or perineal area with fever and/or malaise. Patients should be counseled to hold SGLT2i on sick days (ie, vomiting or diarrhea). However, the SGLT2i groups in the clinical trials were less likely to discontinue drug versus placebo. Lower eGFR also did not result in increased adverse drug reactions and the SGLT2i group had a reduced the risk of AKI.[37] For surgery and procedures requiring one or more days in hospital, or requiring bowel preparation including colonoscopy, stop the SGLT2i at least 3 days pre-procedure (2 days prior to surgery and the day of surgery/procedure) to decrease the risk of DKA. This may require increasing other glucose-lowering drugs during that time. For day procedures, SGLT2i can be stopped on the day of procedure.[40] More details on the use of SGLT2i for the treatment of Type 2 diabetes may be found in Chapter 94.

Mineralcorticoid Receptor Antagonists (MRA)

The concept of aldosterone escape has led to the search for other drug combinations to further suppress the RAAS to improve kidney outcomes. A Cochrane systematic review examined the addition of the MRA spironolactone to an ACEI or ARB in patients with CKD Stage G1-G4.[41] Spironolactone significantly reduced albuminuria and blood pressure but doubled the risk of hyperkalemia and significantly increased the risk of gynecomastia. However, it is unknown whether adding spironolactone or eplerenone to ACEI or ARB will reduce the risk of major CV events or ESKD as a large efficacy

trial in diabetic CKD has never been performed.[42]

Finerenone is a novel, more selective, nonsteroidal MRA. The FIDELIO-DKD trial examined kidney and cardiovascular outcomes in patients with CKD due to Type 2 diabetes (Table 62-6).[38] The risk of hyperkalemia was higher in patients receiving finerenone with an absolute risk increase (ARI) of 12% for serum potassium greater than 5.5 mEq/L (mmol/L) and 3% for serum potassium greater than 6 mEq/L (mmol/L). More patients in the finerenone group needed potassium binding agents for hyperkalemia (307 vs 184 in placebo).[3] Finerenone, unlike spironolactone, is not a blood pressure–lowering drug as mean systolic blood pressure decreased by 2 mm Hg. The patient centric quality of life results of this trial have not been reported yet.[38] Only 4.4% of patients were also on an SGLT2i; therefore, a study examining finerenone in combination with SGLT2i plus ACEI/ARB is ongoing (CONFIDENCE trial). However, finerenone can be considered in patients who cannot tolerate SGLT2i.

Nondinydropyridine Calcium Channel Blockers

Nondihydropyridine calcium channel blockers (diltiazem and verapamil) have yielded beneficial effects on albuminuria, although not as profoundly as ACEIs.[43] The postulated mechanisms for this decrease in kidney injury include suppression of glomerular hypertrophy, inhibition of platelet aggregation, and a decrease in salt accumulation. These agents have been used to reduce albuminuria in combination with an ACEI or ARB even though there are limited data to support this strategy. In general, nondihydropyridine CCBs should be considered fourth-line antiproteinuric drugs when an ACEI/ARB, finerenone SGLT2 inhibitor is contraindicated or not tolerated (Fig. 62-3).[57]

Hypertension

Figure 62-3 provides an algorithm for recommended blood pressure goals based on the degree of albuminuria present and the choice of antihypertensive agent.

The Systolic Blood Pressure Intervention Trial (SPRINT) is the largest trial testing BP targets in CKD. SPRINT assessed whether a lower systolic blood pressure goal of less than 120 mm Hg versus a target of less than 140 mm Hg was desirable.[44] In the 2,646 participants with CKD, the composite renal outcome of a decrease in eGFR of 50% or more or the need for chronic dialysis or kidney transplantation was not significant over the 3.3 years duration of this trial but CV events and all-cause mortality were reduced.[14] Within the CKD subgroup, SPRINT reported no significant difference in serious adverse events. There were increased risks for hypokalemia and hyperkalemia, presumably because of the greater use of antihypertensive medications. Intensive BP lowering increased the risk of AKI in people with moderate CKD (eGFR <45 mL/min/1.73 m^2) and advanced age (>75 years), but the episodes were infrequent and tended to be mild and reversible.[14] There were potential harms to all participants (with and without CKD) in the intensive systolic blood pressure group that included significantly increased risks of syncope, hypotension, electrolyte abnormalities, AKI, and CKD progression.[44] However, the CV and mortality benefits outweigh the risks of harm even in frail and elderly patients.[14]

A SBP target <120 mm Hg may be appropriate in patients who achieve SBP in the 120s without requiring a high number of antihypertensives and who are not experiencing adverse effects of therapy. It is reasonable to consider a change in medications or less-intensive therapy if the patient is symptomatic or BP is excessively low (eg, SBP <100 mm Hg).[14] In practice, adoption of this recommendation in a population of patients with CKD will result in a median SBP around 120 mm Hg, meaning that 50% of patients will have SBP greater than 120 mm Hg.[14] The mean achieved SBP in SPRINT was 121.4 mm Hg.[44] Patients prescribed ACEI/ARBs or diuretics who are targeting an SBP below 120 mm Hg need to be reliable and able to follow instructions to hold these medications when they are unable to maintain adequate fluid intake (eg, vomiting/diarrhea) due to the risk of AKI. The adoption of an SBP target less than 120 mm Hg is an ideal topic for shared decision making between individual patients and clinicians. There is likely to be marked variability in how individual patients weigh and value the potential benefits and harms of intensive BP control. This may vary with age, culture, number of drugs (both BP-lowering and other drugs), and other factors.[14]

Diabetes

Patients with diabetes should be screened annually for CKD starting at the time of diagnosis of Type 2 diabetes and 5 years after the diagnosis of Type 1 diabetes by ordering a serum creatinine, eGFR, and a urine albumin-to-creatinine ratio (ACR).[13]

The management of diabetes in patients with CKD includes reduction of albuminuria and achievement of desired blood pressure and HbA1c (Chapter

94). An individualized HbA1c target ranging from <6.5% (0.065; 48 mmol/mol) to <8.0% (0.08; 64 mmol/mol) is recommended[13] (Evidence Level 1C). Clinicians may consider a target greater than 7% (0.07; 53 mmol/mol) if there is a risk of hypoglycemia, multiple comorbidities, lack of hypoglycemia symptoms or awareness, or limited life expectancy.[13,45] A lower HbA1c target (eg, <6.5% [0.065; 48 mmol/mol] or <7% [0.07; 53 mmol/mol]) is preferred in patients where prevention of complications is the main goal. It should be noted that HbA1c measurements are based on an assumed red blood cell life span of 90 days. In later stage, CKD G4-G5, the red blood cell life span is decreased, so HbA1c values may be falsely low.[45] Hence, in patients with CKD, the HbA1c should be interpreted along with the patient's home blood glucose readings when assessing diabetic control. It is also important to note that patients with CKD G4-G5 are at higher risk of developing hypoglycemia because of the reduction in metabolism of insulin by the kidney as GFR declines. As a result, these patients may require reduced doses of oral or injectable hypoglycemic agents and using agents associated with a lower risk of hypoglycemia (metformin, SGLT2i, GLP-1 receptor agonists, DPP-4 inhibitors). Metformin is still considered a first-line agent in individuals with Type 2 diabetes and CKD[14] (Evidence level 1B). As previously discussed, most patients with CKD due to Type 2 diabetes should also be treated with an SGLT-2 inhibitor if eGFR is greater than or equal to 20 to 25 mL/min/1.73 m^2 and the patient is already receiving an ACEI or ARB. Metformin can be initiated and/or continued in individuals with an eGFR greater than or equal to 30 mL/min/1.73 m^2. The metformin dose should be reduced to 500 mg once or twice daily in patients with an eGFR between 30 and 44 mL/min/1.73 m^2.[46] Metformin is contraindicated in individuals with an eGFR less than 30 mL/min/1.73 m^2 due to the rare but serious risk of lactic acidosis and should be temporarily discontinued before administering contrast agents for imaging studies. Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years, as metformin interferes with intestinal vitamin B12 absorption.[13] Dose adjustments or avoidance of other renally eliminated hypoglycemic agents may also be necessary; the dosing, monitoring, and goals of therapies to treat diabetes mellitus are detailed in Chapter 94.

Evaluation of Therapeutic Outcomes

Frequency of laboratory and urine testing based on CKD category and degree of albuminuria as defined by KDIGO are shown in Table 62-4. The monitoring necessary for patients with hypertension and diabetes is the same in the CKD population as it is in the non-CKD population.

CONCLUSION

The prevalence of CKD continues to increase especially in high-risk populations. Although efforts to delay progression of CKD, including prudent use of ACEI/ARB and SGLT2i in diabetic patients are paramount, measures to diagnose and manage the associated secondary complications and comorbid conditions early in the course of the disease are also essential.

A multidisciplinary team structure is a rational approach to effectively design and implement individual patient care plans often required in the CKD population given the extensive nonpharmacologic and pharmacologic interventions. Pharmacists are well positioned to actively participate in the chronic disease and medication management of ambulatory CKD patients as well as those who are hospitalized.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
ACR	urinary albumin-to-creatinine ratio
AKI	acute kidney injury
ARB	angiotensin receptor blocker
ATII	angiotensin II
CCB	calcium channel blocker
CKD	chronic kidney disease

CKD-EPI equation	Chronic Kidney Disease Epidemiology Collaboration equation
CREDENCE	Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy
CV	cardiovascular
CVD	cardiovascular disease
Dapa-CKD	Dapagliflozin in Patients with Chronic Kidney Disease
DKA	diabetic ketoacidosis
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FIDELIO-DKD	Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes
GFR	glomerular filtration rate
HbA1c	glycated hemoglobin or hemoglobin A_{1c}
KDIGO	Kidney Disease: Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease
MRA	mineralcorticoid receptor antagonist
NNT	number needed to treat
PIGN	post-infectious glomerulonephritis
PTH	parathyroid hormone
RAAS	renin–angiotensin–aldosterone system
Scr	serum creatinine
SGLT2i	sodium glucose transport-2 inhibitors
SPRINT	Systolic Blood Pressure Intervention Trial

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* 2013;3:1–150.

2. US Department of Health and Human Services. Healthy People 2020 Objectives for Chronic Kidney Disease. Available at: http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=6. Accessed February 28, 2022.

3. Raj R. Can Finerenone Fiddle the Forgotten A of the RAAS String? Available at: http://www.nephjc.com/news/fidelio. Accessed June 25, 2021.

4. United States Renal Data System. 2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2019. Available at: https://www.usrds.org/annual-data-report/. Accessed June 25, 2021.

5. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD Incidence and prevalence in the United States through 2030. *J Am Soc Nephrol.* 2019;30(1):127–135. 10.1681/asn.2018050531

6. United States Renal Data System, 2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

7. Hounkpatin HO, Fraser SDS, Honney R, Dreyer G, Brettle A, Roderick PJ. Ethnic minority disparities in progression and mortality of pre-dialysis chronic kidney disease: A systematic scoping review. *BMC Nephrol.* 2020;21(1):217. 10.1186/s12882-020-01852-3

8. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol.* 2016;27(9):2576–2595. 10.1681/asn.2016010027

9. Robles-Osorio ML, Sabath E. Social disparities, risk factors and chronic kidney disease. *Nefrol (English Ed).* 2016;36(5):577–579. 10.1016/j.nefroe.2016.05.004

10. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63(5):713–735. 10.1053/j.ajkd.2014.01.416

11. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA.* 2011;305(15):1553–1559. 10.1001/jama.2011.451

12. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: A meta-analysis. *JAMA.* 2016;315(2):164–174. 10.1001/jama.2015.18202

13. Caramori ML, Chan JCN, Heerspink HJL, et al. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int.* 2020;98(4S):S1–S115. 10.1016/j.kint.2020.06.019

14. Cheung AK, Chang TI, Cushman WC, et al. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int.* 2021;99(3S):S1–S87. 10.1016/j.kint.2020.11.003

15. Orth SR, Hallan SI. Smoking: A risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients: Absence of evidence or evidence of absence? *Clin J Am Soc Nephrol.* 2008;3(1):226–236. CJN.03740907

16. Hogan SL, Vupputuri S, Guo X, et al. Association of cigarette smoking with albuminuria in the United States: The third National Health and Nutrition Examination Survey. *Ren Fail*. 2007;29(2):133–142. 10.1080/08860220601098888

17. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med.* 2006;144(1):21–28. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16389251

18. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. *J Am Soc Nephrol.* 2006;17(6):1695–1702. 10.1681/asn.2005060638

19. Chang Y, Ryu S, Choi Y, et al. Metabolically healthy obesity and development of chronic kidney disease: A cohort study. *Ann Intern Med.* 2016;164(5):305–312. 10.7326/M15-1323

20. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2009;4(10):1565–1574. doi: 10.2215/CJN.02250409 [doi]

21. Gajjala PR, Sanati M, Jankowski J. Cellular and molecular mechanisms of chronic kidney disease with diabetes mellitus and cardiovascular diseases as its comorbidities. *Front Immunol.* 2015;6:340. 10.3389/fimmu.2015.00340

22. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol.* 2006;17(11):2974–2984. 10.1681/asn.2006040377

23. Wang SM, Hsiao LC, Ting IW, et al. Multidisciplinary care in patients with chronic kidney disease: A systematic review and meta-analysis. *Eur J Intern Med.* 2015;26(8):640–645. 10.1016/j.ejim.2015.07.002

24. Filler G, Lipshultz SE. Why multidisciplinary clinics should be the standard for treating chronic kidney disease. *Pediatr Nephrol.* 2012;27(10):1831–1834. 10.1007/s00467-012-2236-3

25. St. Peter WL, Wazny LDD, Patel UDD, St Peter WL, Wazny LDD, Patel UDD. New models of chronic kidney disease care including pharmacists: Improving medication reconciliation and medication management. *Curr Opin Nephrol Hypertens.* 2013;22(6):656–662. 10.1097/MNH.0b013e328365b364

26. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev.* 2006;(4)(4):CD006257. doi: 10.1002/14651858.CD006257

27. Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease (STOP ACEi). Available at: https://www.birmingham.ac.uk/research/bctu/trials/renal/stopacei/index.aspx. Accessed June 25, 2021.

28. Tylicki L, Lizakowski S, Rutkowski B. Renin-angiotensin-aldosterone system blockade for nephroprotection: Current evidence and future directions. *J Nephrol.* 2012;25(6):900–910. 10.5301/jn.5000134

29. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547–553. 10.1016/s0140-6736(08)61236-2

30. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2013;369(20):1892–1903. 10.1056/NEJMoa1303154

31. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med.* 2012;367(23):2204–2213. 10.1056/NEJMoa1208799

32. Imai E, Haneda M, Yamasaki T, et al. Effects of dual blockade of the renin-angiotensin system on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy and hypertension in the ORIENT: A post-hoc analysis (ORIENT-Hypertension). *Hypertens Res.* 2013;36(12):1051–1059. 10.1038/hr.2013.86;10.1038/hr.2013.86

33. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436–1446. 10.1056/NEJMoa2024816

34. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295–2306. 10.1056/NEJMoa1811744

35. Musso G, Sircana A, Saba F, Cassader M, Gambino R. Assessing the risk of ketoacidosis due to sodium-glucose cotransporter (SGLT)-2 inhibitors in patients with type 1 diabetes: A meta-analysis and meta-regression. *PLOS Med.* 2020;17(12):e1003461. doi: 10.1371/journal.pmed.1003461

36. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 inhibitor–associated diabetic ketoacidosis: Clinical review and recommendations for prevention and diagnosis. *Clin Ther.* 2016;38(12):2654–2664.e1. doi: 10.1016/j.clinthera.2016.11.002

37. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2019;7(11):845–854. 10.1016/S2213-8587(19)30256-6

38. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(23):2219–2229. 10.1056/NEJMoa2025845

39. Unnikrishnan A, Kalra S, Purandare V, Vasnawala H. Genital infections with sodium glucose cotransporter-2 inhibitors: Occurrence and management in patients with type 2 diabetes mellitus. *Indian J Endocrinol Metab.* 2018;22(6):837. 10.4103/ijem.IJEM_159_17

40. Society AD. ALERT UPDATE January 2020 Periprocedural Diabetic Ketoacidosis (DKA) with SGLT2 Inhibitor Use. 2020. Available at: https://diabetessociety.com.au/documents/ADS_DKA_SGLT2i_Alert_update_2020.pdf. Accessed June 25, 2021.

41. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev.* 2014;4:Cd007004. 10.1002/14651858.CD007004.pub3

42. Hou J, Xiong W, Cao L, Wen X, Li A. Spironolactone add-on for preventing or slowing the progression of diabetic nephropathy: A meta-analysis. *Clin Ther.* 2015;37(9):2086–2103 e10. doi: 10.1016/j.clinthera.2015.05.508

43. Hart P, Bakris GL. Calcium antagonists: Do they equally protect against kidney injury? *Kidney Int.* 2008;73(7):795–796. 10.1038/sj.ki.5002773

44. Wright JT Jr., Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;373(22):2103–2116. 10.1056/NEJMoa1511939

45. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: A report from an ADA Consensus Conference. *Am J Kidney Dis.* 2014;64(4):510–533. 10.1053/j.ajkd.2014.08.001

46. Lalau J-D, Kajbaf F, Bennis Y, Hurtel-Lemaire A-S, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. *Diabetes Care*. 2018;41(3):547–553. 10.2337/dc17-2231

SELF-ASSESSMENT QUESTIONS

1. Risk factors for the development of CKD include which of the following:

   A. Family history of CKD and diabetes

   B. Obesity and hypertension

   C. Low-birth weight and low education level

   D. All of the above

2. A 51-year-old female with an eGFR of 37 mL/min/1.73 m^2 and a urinary albumin-to-creatinine (ACR) ratio of 20 mg/g (2.3 mg/mmol) would be classified in which albuminuria and KDIGO category of CKD?

   A. G3a, A1

   B. G3a, A2

   C. G3b, A1

D. G3b, A2

3. A 44-year-old female with a history of CKD due to type 2 diabetes presents to your primary care clinic. Her most recent ACR is 113 mg/g (12.8 mg/mmol), her eGFR is 44 mL/min/1.73 m^2, and blood pressure is 137/88 mm Hg. She is on chlorthalidone 12.5 mg po daily as her only antihypertensive drug. Which one of the following recommendations is most appropriate?

   A. No changes, blood pressure is at target

   B. Start dapagliflozin 10 mg po daily

   C. Start ramipril 2.5 mg po daily

   D. Start amlodipine 5 mg po daily

4. Patients with CKD who have severe vomiting, diarrhea, or are dehydrated should be instructed to hold which of the following medications?

   A. Enalapril

   B. Metformin

   C. Dapagliflozin

   D. All of the above

5. Hypertensive patients with CKD should limit dietary sodium to which of the following?

   A. <1 g/day

   B. <1.5 g/day

   C. <2 g/day

   D. <2.5 g/day

6. According to the KDIGO guideline, what is the blood pressure target in a patient with CKD and a urinary albumin-to-creatinine (ACR) of 22 mg/g (2.5 mg/mmol)?

   A. SBP<120 mm Hg

   B. SBP <130 mm Hg

   C. SBP<135 mm Hg

   D. SBP <140 mm Hg

7. A 67-year-old female with urinary albumin-to-creatinine ratio (ACR) of 55.4 mg/g (6.3 mg/mmol), a serum potassium of 4.5 mEq/L (mmol/L), and an eGFR of 38 mL/min/1.73 m^2 is started on irbesartan 75 mg po once daily. The serum creatinine and potassium levels should be monitored at what time point after initiation of therapy?

   A. In 2 days

   B. In 1 week

   C. Within 2 to 4 weeks

   D. Within 4- to 2 weeks

8. A patient with type 2 diabetic CKD is receiving candesartan 32 mg po daily. Their eGFR is 27 mL/min/1.73 m^2 and ACR is 221 mg/g (25 mg/mmol) despite the ARB. Which class of medications should be considered next?

   A. MRA

   B. SGLT2i

   C. ACEI

   D. Nondihydropyridine CCB

9. Patients receiving SGLT2i should be counseled on which of the following adverse effects?

   A. Risk of increased mycotic genital infections

   B. Risk of euglycemic DKA

   C. Rick of urinary tract infections

   D. All of the above

10. A patient receiving canagliflozin 100 mg po daily for treatment of diabetic CKD returns to clinic and their eGFR has decreased to 12 mL/min/1.73 m^2. What should be done with their canagliflozin?

    A. Discontinue canagliflozin

    B. Decrease dose to 50 mg po daily

    C. Continue same dose

    D. Switch to dapagliflozin

11. ACEI or ARBs should be held when which of the following occurs?

    A. Stage G5 with uremic symptoms

    B. Serum potassium >6 mEq/L (mmol/L)

    C. Scr increases >50%

    D. All of the above

12. Contraindications to the use of ACEI or ARB include which of the following?

    A. Pregnancy or wanting to become pregnant

    B. Bilateral renal artery stenosis

    C. Cough

    D. Both A and B

13. Finerenone is a treatment option for patients with diabetic CKD. Which of the following characteristics best describe this drug?

    A. Associated with hyperkalemia

    B. Lowers blood pressure

C. Reduces CV events

D. Both A and C

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** All of the factors listed increase risk for the development of CKD. See Table 62-1 for more information.
2. **C.** The patient would be classified as G3b, A1. See Fig. 62-1.
3. **C.** Patient is in Stage G3b, A2, so starting an ACEI or ARB is recommended. The SBP target for most CKD patients based on the SPRINT trial is <120 mm Hg. An ACEI or ARB should be started and titrated to the maximally tolerated dose before adding an SGLT2i to treat her diabetic CKD. See Fig. 62-3 for more information.
4. **D.** Sick day medications include ACEI/ARBs, diuretics, metformin, SGLT2i, sulfonylureas, NSAIDs, or COX 2 inhibitors.
5. **C.** See information related to nonpharmacologic therapies in Table 62-2.
6. **A.** The 2021 KDIGO Blood Pressure in CKD guideline now suggests a target SBP<120 mm Hg in most patients based on the results from the SPRINT trial; however, individual patient characteristics and patient preference should be used before targeting intensive therapy. See Fig. 62-3 for more information.
7. **C.** If eGFR 30 to 59 mL/min/1.73 m^2, repeat Scr and serum potassium in 2 to 4 weeks. See Table 62-5 for more information.
8. **B.** SGLT2i should be considered in patients with diabetic CKD due to Type 2 diabetes and maximally tolerated doses of ACEI or ARB with ACR>200 mg/g (22.6 mg/mmol) and eGFR ≥20 to 25 mL/min/1.73 m^2.
9. **D.** SGLT2i treatments have been associated with all of the adverse effects listed.
10. **C.** Once started, SGLT2i should be continued until dialysis or kidney transplantation as was done in the CREDENCE and Dapa-CKD trials (see Table 62-5).
11. **D.** It is reasonable to discontinue ACEI or ARB treatment temporarily with the aim of increasing eGFR to hold off starting renal replacement therapy in patient with Stage G5 with uremic symptoms. In patients with K>6 mEq/L (mmol/L), the ACEI or ARB should be held until the K+ is treated and a K+ <5.5 mEq/L (mmol/L) is consistently achieved (see Table 62-6). If Scr increase is >50%, the ACEI/ARB should be stopped (see Table 62-6).
12. **D.** Pregnancy is a contraindication as ACEI and ARB therapy can affect the developing fetus' kidneys, especially in the second and third trimesters. Bilateral renal artery stenosis will cause the eGFR to decrease dramatically since angiotensin II constricts the efferent arteriole and blocking it will cause the efferent arteriole to dilate. Renal artery stenosis patients rely upon that efferent constriction to maintain normal glomerular pressures for filtration (Figure 62-3). Cough is a side effect of ACEI inhibitors due to the accumulation of bradykinin but this side effect is not associated with ARBs.
13. **D.** Finerenone is a nonsteroidal, more selective MRA but is still associated with hyperkalemia. It is not an effective blood pressure lowering agent as patients in the FIDELIO-DKD trial exhibited reductions in SBP of 2 mm Hg. FIDELIO-DKD also showed that this drug lowered CV events as a secondary endpoint (see Table 62-5).