Chapter 63: Chronic Kidney Disease: Management of Secondary Complications

Joanna Q. Hudson

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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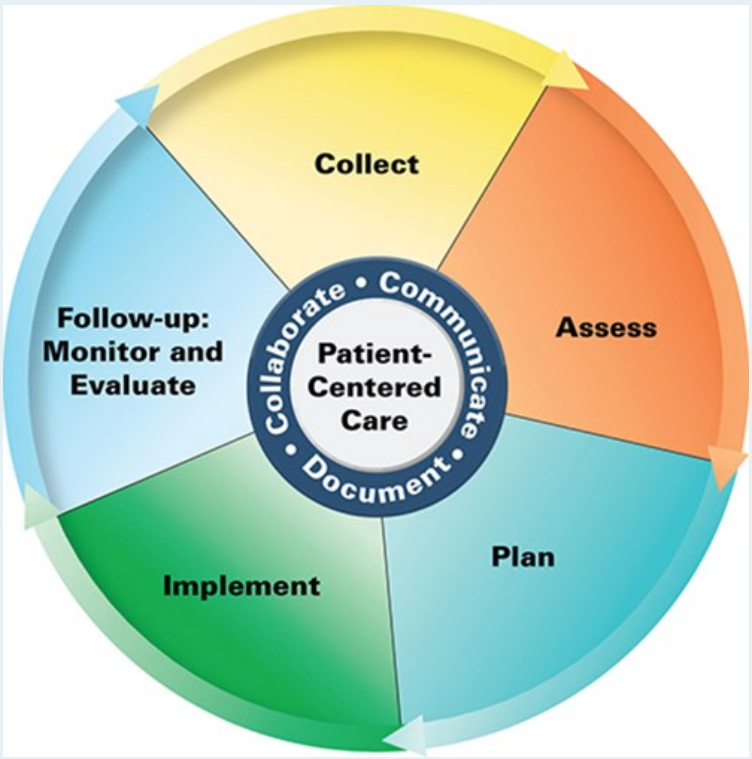
1. Chronic kidney disease (CKD) affects many other organ systems leading to secondary complications. The most common complications include fluid and electrolyte disorders, anemia, mineral and bone disorder, metabolic acidosis, and increased incidence of cardiovascular disease.
2. Anemia of CKD is multifactorial with loss of erythropoietin synthesis by the kidney, iron deficiency, and chronic inflammation all implicated.
3. CKD-mineral and bone disorder (CKD-MBD) includes abnormalities in parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), phosphorus, calcium, vitamin D, and bone turnover, and contributes to soft-tissue and extravascular calcifications.
4. 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 complications of CKD.
5. Patient education, an interdisciplinary team, and shared decision making play critical roles in the appropriate management of complications of CKD.
6. Management of anemia includes administration of erythropoiesis-stimulating agents (ESAs) and regular iron supplementation to maintain the target hemoglobin concentration and prevent the need for blood transfusions. There is a higher risk of cardiovascular events when ESAs are used to target hemoglobin values greater than 11 g/dL (110 g/L; 6.83 mmol/L).
7. Management of CKD-MBD includes dietary phosphorus restriction, phosphate-binding agents, activated vitamin D supplementation, and calcimimetic therapy.
8. Initiation of statins for primary prevention of hyperlipidemia in patients receiving dialysis is not recommended due to a lack of benefit from randomized controlled trials and meta-analyses, while benefit still may exist in those with non-dialysis dependent CKD.
9. CKD-associated pruritus is a secondary complication that significantly affects patients' quality of life and has limited treatment options. Difelikefalin is a selective kappa opioid receptor agonist with antipruritic effects approved for pruritus in hemodialysis patients and is the only approved treatment option.

PATIENT CARE PROCESS

Patient Care Process for Secondary Complications of Chronic Kidney Disease (CKD)



Collect

- Patient characteristics (eg, age, sex, CKD stage [see Chapter 62], medication allergies)
- Past medical history
- Social history (eg, smoking), family/friend supports
- Dietary intake (eg, phosphate-containing foods/sources, iron sources, sodium intake)
- Current medications including OTC medications, herbals, dietary supplements
- Objective data:
  - Blood pressure, heart rate, weight
  - Labs as defined under “Assess”

Assess

- CKD stage (see Chapter 62 for staging criteria)
- Reported symptoms: see Clinical Presentation for signs and symptoms of secondary complications
- Serum potassium concentration—assess frequently in CKD stage 4, 5, and end-stage kidney disease (ESKD)
- Volume status—peripheral and pulmonary edema versus hypovolemia (may need to alter diuretic regimen)
- Hemoglobin concentration (see Table 63-2 for ESA initiation)
- Iron indices (transferrin saturation and ferritin) for patients on an ESA, assess transferrin saturation (TSAT) and ferritin at least every 3 months

and assess when clinically indicated (eg, following blood loss)

- Concentrations of calcium, albumin (to calculate corrected calcium), phosphorus, and parathyroid hormone (PTH) (see Table 63-6)
- Insurance coverage of medications, current out of pocket cost of medications
- Medication adherence
- Other recommendations as outlined in Chapter 62

Plan

- Drug therapy recommendations, including dose, route, frequency, and duration
- Dietary recommendations (consider sodium, potassium, phosphorus, and fluid intake)
- Monitoring parameters, including frequency and timing of follow-up
- Patient education, including purpose of new or changed treatment, lifestyle modifications, medication administration (eg, timing of phosphate binders with meals), injection technique
- Self-monitoring for resolution of symptoms
- Referrals to other providers when appropriate (eg, clinical pharmacist, dietitian, nephrologist, nephrology nurse, social worker, endocrinologist)

Implement*

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

Follow-up: Monitor and Evaluate

- Resolution of symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

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

BEYOND THE BOOK

BEYOND THE BOOK

Read and evaluate the case presented in Chapter 56—End-Stage Kidney Disease: Urine Trouble Level II. In: Schwinghammer TL, Koehler JM, Borchert JS, Slain D, Park SK. eds. *Pharmacotherapy Casebook: A Patient-Focused Approach*, 11e. Mcgraw Hill; 2020. Available at https://accesspharmacy.mhmedical.com/content.aspx?bookid=2868&sectionid=242182546.

This activity is useful to enhance student understanding regarding the COLLECT, ASSESS, PLAN, and IMPLEMENT steps in the patient care process.

INTRODUCTION

Chronic kidney disease (CKD) affects many organ systems and processes leading to secondary complications. While the primary goal is to prevent CKD progression and the resultant complications (see Chapter 62 for a more in-depth discussion of CKD progression and management), ultimately many individuals progress to the more advanced stages of CKD (CKD G4—end-stage kidney disease, ESKD). The most common complications of CKD include fluid and electrolyte disorders (hypervolemia, hyperkalemia), anemia, mineral and bone disorder, metabolic acidosis, and increased incidence of cardiovascular disease (CVD). Complications of CKD are frequently unrecognized or are inappropriately managed, and for many patients, this contributes to significant morbidity, premature mortality, or a poorer prognosis if and when they require renal replacement therapy. This chapter primarily covers the pathophysiology and treatment of anemia, CKD-mineral and bone disorder (CKD-MBD), select cardiovascular complications, and CKD-associated pruritus in adult patients with CKD. The reader is referred to Chapters 68, 70, and 71 for a more detailed discussion of management and monitoring strategies for CKD patients with hypervolemia, hyperkalemia, and metabolic acidosis, respectively. A list of complications of advanced CKD is provided in Table 63-1.

TABLE 63-1

Complications of Chronic Kidney Disease[a]

Organ System or Complication	Clinical Manifestations[a]
Amyloidosis	Accumulation of β_2-microglobulin Carpal tunnel syndrome
Cardiovascular disease	Atherosclerosis-related complications (arrhythmias, heart failure, myocardial infarction, stroke)
Endocrine	Hypoglycemic episodes (result of decreased degradation of insulin by the kidney)
Gastrointestinal	Nausea, vomiting, anorexia (from uremia) Delayed gastric emptying Gastroesophageal reflux GI bleeding
Hematologic	Anemia Bleeding diathesis Platelet dysfunction
Hyperkalemia	Arrhythmias/ECG changes Metabolic acidosis Muscle weakness or paralysis
Hypervolemia	Edema Heart failure Hypertension
Immune disorders	Impaired cell-mediated immunity Lymphopenia

Metabolic acidosis	Bone disease Hyperkalemia Reduced respiratory reserve Skeletal muscle catabolism
Mineral and bone disorder	Bone fractures Calciphylaxis
Neurologic	Peripheral neuropathies Restless leg syndrome Uremic encephalopathy
Protein–energy wasting	Malnutrition
Uremic pruritus	Generalized itching predominantly of back, face, and extremity used for vascular access, but may affect any area (May be more severe during or immediately after hemodialysis)

ECG, electrocardiogram.

[a]Not all inclusive.

EPIDEMIOLOGY

Anemia of Chronic Kidney Disease

As a common complication of CKD, anemia prevalence increases with age in individuals with non-dialysis (ND) CKD with reports of 50% prevalence in older Medicare patients (aged 66-85 years) and 28% in younger individuals (aged 18-63 years).[1] This prevalence increases as CKD progresses with estimates of 44% in CKD G3 increasing to 73% in CKD G5 for the older individuals and 22% increasing to 54% in the younger individuals. Despite the fact that anemia is a well-recognized complication of CKD, management is suboptimal, particularly in the ND-CKD population where patients who meet criteria for treatments including erythropoiesis stimulating agents (ESAs) and iron often do not receive an intervention.[2] This is supported by the fact that the average hemoglobin (Hb) among incident (new) ESKD patients in the United States in 2018 was 9.3 g/dL (93 g/L; 5.77 mmol/L) with levels less than 9 g/dL (90 g/L; 5.59 mmol/L) in many areas throughout the United States. Only 14.6% of incident patients had received an ESA prior to ESKD.[3] Furthermore, iron deficiency is present in more than half of ND-CKD patients and up to 25% of dialysis patients, in part, due to the fact that iron supplementation is not a standard treatment approach for ND-CKD patients.[4] For prevalent dialysis patients (on dialysis for at least 90 days), the majority of patients maintain Hb levels between 10 and 11.9 g/dL (100 and 119 g/L; 6.21 and 7.39 mmol/L), due in large part to protocol- driven approaches that lead to ESA and iron use.[5] This does not negate the fact that suboptimal anemia management at initiation of dialysis is associated with increased morbidity, even if corrected in the subsequent months after dialysis initiation.[6] Anemia of CKD is also associated with increased morbidity with greater likelihood of hospitalization, cardiovascular (CV) disease, cognitive impairment, and decreased quality of life.[7]

Chronic Kidney Disease–Related Mineral and Bone Disorder

CKD-MBD collectively includes abnormalities in parathyroid hormone (PTH), calcium, phosphorus, active vitamin D, and fibroblast growth factor 23 (FGF23) and is considered one of the most common CKD-related secondary complications with significant implications on patient morbidity and

mortality. Abnormalities in these parameters, particularly elevations in PTH and FGF23, may be observed in earlier stages of CKD (stage G3) with hyperphosphatemia and calcium abnormalities more prevalent as kidney function declines to stage G4.[8,9] Data regarding prevalence are limited in the ND-CKD population. Based on data from dialysis patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS) approximately 24% of ESKD patients on HD have hyperparathyroidism (defined as a PTH >600 pg/mL [ng/L; 64.2 pmol/L]) and 43% have phosphorus above goal (phosphorus >5.6 mg/dL [1.81 mmol/L]).[5] CKD-MBD worsens as kidney function declines with more resistant disease associated with worsening kidney function.[9] Severity of this secondary complication is also indicated by control of associated parameters (PTH, albumin corrected calcium and phosphorus) and use of pharmacologic therapy. Based on data from US hemodialysis patients, approximately 70% of patients had at least one parameter out of control PTH (>600 pg/mL [ng/L; 64.2 pmol/L], corrected calcium >10.2 mg/dL [2.55 mmol/L], serum phosphorus >5.5 mg/dL [1.78 mmol/L]).

ETIOLOGY AND PATHOPHYSIOLOGY

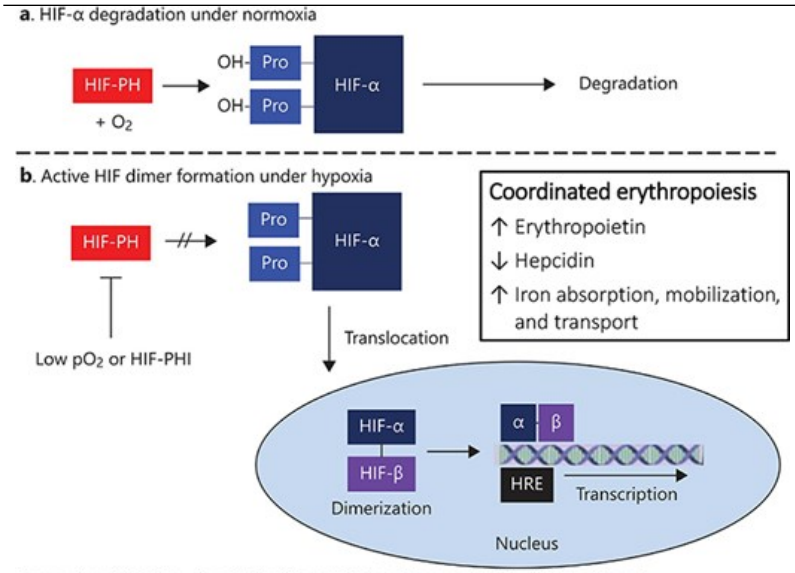
Anemia of Chronic Kidney Disease

The primary cause of anemia of CKD is a relative deficiency in production of erythropoietin by interstitial fibroblasts in the outer renal cortex and medulla of the kidney where approximately 90% of production occurs (the remainder occurs in the liver). Erythropoietin is a glycoprotein hormone that stimulates erythropoiesis (red blood cell production) by binding to receptors on early erythroid progenitor cells, burst-forming units, and colony-forming units in the bone marrow, thus preventing apoptosis and allowing cell division and maturation into mature red blood cells. In individuals with normal kidney function, plasma concentrations of erythropoietin increase exponentially in response to hypoxia to promote erythropoiesis; however, this response is lost as kidney disease progresses.[10]

Impaired oxygen sensing in the kidneys leads to disrupted signaling of specific hypoxia inducible factors (HIFs). HIF is a transcription factor composed of oxygen regulated α subunits (HIF-1α and HIF-2α) and a β subunit. The β subunit is present consistently in the HIF complex and binds with one of the three isoforms of the α subunit to induce expression of target genes depending on the complex formed. Erythropoietin gene transcription for all hypoxia-induced genes is initiated by HIF-α with the HIF-2α subunit being the main subunit involved in erythropoietin production and iron transport. In the presence of normal oxygen levels, an enzyme known as HIF-prolyl hydroxylase (HIF-PH) is activated and causes HIF-α to be hydroxylated which leads to its degradation and no stimulation of erythropoietin production by erythropoietin producing cells. In hypoxic conditions, the HIF-PH enzyme is inactive allowing HIF-α to translocate to the cell nucleus where it forms a heterodimer with the β subunit causing activation of gene transcription to increase erythropoietin production, promote iron absorption and transport, and decrease hepcidin levels. This is a nicely regulated system that is altered in CKD. With CKD, oxygen consumption in the kidneys is decreased due to disease-related changes (Fig. 63-1). Despite the fact that hypoxia is present systemically, the erythropoietin producing cells do not detect the extent of hypoxia since there is sufficient oxygen in the immediate environment (in the kidney relative to oxygen needs). This results in a disruption in HIF signaling and a relative deficiency in erythropoietin production.[11-13]

FIGURE 63-1

HIF activity under normoxia and hypoxia. Under normoxia (normal oxygen conditions) oxygen binds with the HIF-PH enzyme to form a complex with HIF-α which is then degraded. With hypoxia (reduced oxygen conditions) the HIF-PH enzyme is inactive and the HIF-α subunit can translocate to the cell nucleus where it forms a heterodimer with the β subunit. This leads to gene transcription and expression of multiple genes resulting in increased endogenous erythropoietin production, decreased hepcidin, and improved iron absorption, mobilization, and transport. (HIF-PH, hypoxia inducible factor prolyl hydroxylase enzyme; HRE, HIF responsive element, Pro, proline.) *(Reprinted, with permission, from Locatelli F, Fishbane S, Block GA, MacDougall IC. Targeting hypoxia-inducible factors for thetreatment of anemia in chronic kidney disease patients. Am J Nephrol. 2017;45:187–199.)*



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*

In addition to impaired erythropoietin production, iron deficiency is common in individuals with advanced kidney disease (ie, CKD stages G4, G5, and ESKD) due to decreased gastrointestinal (GI) absorption of iron, inflammation, frequent blood testing, blood loss from hemodialysis (HD) for patients with ESKD, and increased iron demands from ESA therapy when treatment is initiated. Iron deficiency is the leading cause of resistance to ESAs and the reason frequent iron supplementation is necessary.[10,14] Hepcidin, a hormone produced by the liver, is a primary regulator of iron homeostasis. This hormone directly binds to and inhibits the protein ferroportin that transports iron out of storage cells and into circulation. When iron stores are high, hepcidin production is increased and results in a decrease in intestinal iron absorption, impairment of iron recycling from macrophages, and decreased mobilization of stored iron from hepatocytes. Hepcidin production is also induced by inflammation or infection. As a result, the increase in hepcidin in inflammatory conditions leads to sequestering of iron, decreased iron absorption, and ineffective red blood cell production. Conversely, hepcidin production is decreased when iron stores are low. The fact that hepcidin plays such a role in iron regulation has prompted the development of agents to target hepcidin and potentially alter iron transport.[15]

Additional factors contributing to the development of anemia of CKD are the decreased red cell life span (from the normal 120 days to approximately 60 days in individuals with CKD 5D), the effects of accumulation of uremic toxins and inflammatory cytokines, and vitamin B_{12} and folate deficiencies.

Chronic Kidney Disease–Related Mineral and Bone Disorder

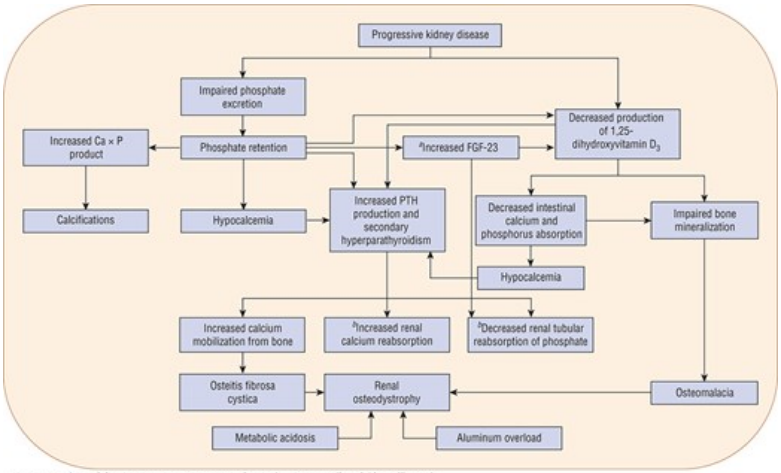
3 Disorders of mineral and bone metabolism are common in the CKD population and include abnormalities in PTH, calcium, phosphorus, vitamin D, fibroblast growth factor-23 (FGF-23), bone turnover, as well as soft-tissue calcifications. These abnormalities have been described as characteristics of secondary hyperparathyroidism (sHPT) and renal osteodystrophy (ROD). The term CKD-MBD encompasses these abnormalities in mineral and bone metabolism as well as associated calcifications.

The pathophysiology of CKD-MBD is complex (Fig. 63-2). Calcium and phosphorus homeostasis is mediated through the effects of PTH, 1,25-dihydroxyvitamin D_3 (calcitriol), and FGF-23 on bone, the GI tract, kidney, and the parathyroid gland. As kidney function declines, there is a decrease in phosphate elimination, which results in hyperphosphatemia and a decrease in serum calcium concentration. Hypocalcemia is the primary stimulus for secretion of PTH by the parathyroid glands. Hyperphosphatemia also increases PTH synthesis and release through its direct effects on the parathyroid gland and production of prepro-PTH messenger RNA.[16] In an attempt to normalize ionized calcium, PTH increases calcium reabsorption by the distal tubules and decreases phosphate reabsorption in the proximal tubules of the kidney (at least until the GFR falls to less than 30 mL/min/1.73 m^2 [0.29 mL/s/m^2]) and also increases calcium mobilization from bone. FGF-23 production in bone also increases in response to high phosphate levels and increased PTH and promotes phosphate excretion by the kidney. The result is a relative normalization of calcium and phosphorus, at least in the early stages of CKD; however, this occurs at the expense of an elevated PTH and FGF-23 ("the trade-off hypothesis"). The increase in PTH is most notable when GFR is less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2) (CKD G3a and higher) and worsens as kidney function further declines.[16] With advanced

kidney disease, the kidney fails to respond to PTH or to FGF-23 and abnormalities in calcium and phosphorus worsen. Over time the negative effects of sustained hyperparathyroidism on bone are realized as calcium resorption from bone persists.

FIGURE 63-2

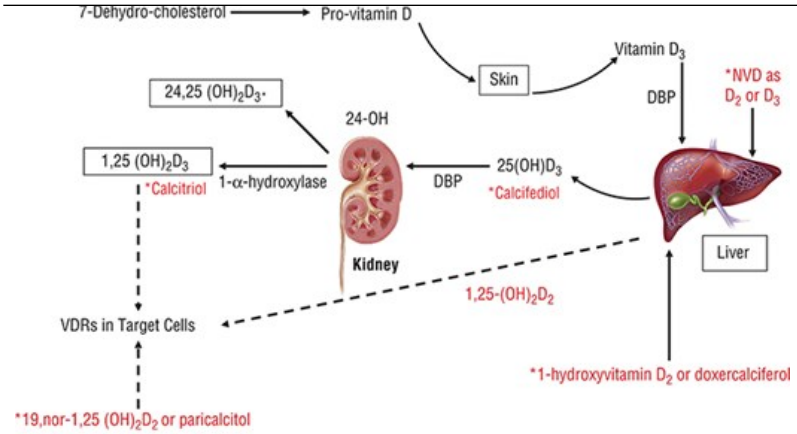
Pathophysiology of CKD-MBD. (Ca, calcium; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.) [a]FGF-23 also increases in response to 1,25-dihydroxyvitamin D_3. [b]These adaptations are lost as kidney disease progresses.



1,25-Dihydroxyvitamin D_3 or calcitriol promotes increased intestinal absorption of calcium and phosphorus, which helps normalize ionized calcium. Calcitriol also works directly on the parathyroid gland to suppress PTH production. The enzyme 1-α-hydroxylase is responsible for the final hydroxylation and conversion of the vitamin D precursor, 25-hydroxyvitamin D or 25(OH)D, to calcitriol in the kidney (Fig. 63-3). As kidney disease progresses, the concentrations of calcitriol decline due to loss of 1-α-hydroxylase activity. The resultant vitamin D deficiency leads to reduced intestinal calcium and phosphorus absorption and worsening hyperparathyroidism. Increases in FGF-23 also promote calcitriol deficiency.[16] Calcitriol deficiency is more prevalent in individuals with CKD G4-G5. Deficiency in 25(OH)D (levels of <30 ng/mL [75 nmol/L]) is also common in individuals with CKD due to decreased dermal synthesis of vitamin D, decreased exposure to sunlight, and reduced dietary intake of vitamin D.

FIGURE 63-3

Vitamin D metabolism. Production of active vitamin D requires conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D_3) by sunlight, followed by the first hydroxylation step in the liver to form 25-hydroxyvitamin D_3 or 25(OH)D_3, and the final conversion step in the kidney to form 1,25-dihydroxyvitamin D_3 or calcitriol. Within the kidney vitamin D may also be converted to an inactive form 24,25(OH)D_3. *Vitamin D therapies include calcitriol which is the active compound 1,25$(OH)_2D_3$ made endogenously, nutritional vitamin D (NVD) as ergocalciferol (a D_2 compound) or cholecalciferol (a D_3 compound), calcifediol which is 25(OH)D_3, and the vitamin analogs paricalcitol and doxercalciferol. If NVD is administered, the compound requires conversion to the active form as either a 1,25(OH)D_2 (as with ergocalciferol) or a 1,25(OH)D_3 (as with cholecalciferol). Calcitriol and paricalcitol are active as given. Doxercalciferol requires conversion to the active form [1,25$(OH)_2D_2$] by the liver. Agents in red are vitamin D agents. (DBP, vitamin D binding protein; NVD, nutritional vitamin D; VDRs, vitamin D receptors.)



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 abnormalities of CKD-MBD lead to alterations in structural integrity of bone and other associated consequences. The continuous high rate of production of PTH by the parathyroid glands promotes parathyroid hyperplasia. Nodular tissue demonstrates more rapid growth potential and is associated with fewer vitamin D and calcium-sensing receptors, resulting in resistance to exogenous calcitriol therapy. Bone abnormalities are almost universal in dialysis patients and observed in the majority of those with CKD G3-G5.[17] The bone abnormalities include osteitis fibrosa cystica (high bone turnover disease), osteomalacia (low bone turnover disease), and adynamic bone disease. Osteitis fibrosa cystica is most common and is characterized by areas of peritrabecular fibrosis. Bone marrow fibrosis and decreased erythropoiesis are also consequences of severe osteitis fibrosa cystica. Osteomalacia was historically noted in HD patients with aluminum toxicity, a finding less common today due to the decreased use of aluminum-containing phosphate binders and changes in the processing of dialysate solutions to decrease aluminum content. Adynamic lesions are characterized by low amounts of fibrosis or osteoid tissue and low bone formation rates. Multiple risk factors for the development of this bone disease include high concentrations of dialysate calcium along with high doses of calcium-containing phosphate binders, aggressive management with vitamin D therapy, diabetes, and aluminum toxicity.[16]

The morbidity and mortality of CKD patients are increased in individuals with both severe hypo- and hyperparathyroidism.[17] Elevations of serum phosphorus, even within the upper limits of the normal range, have been associated with increased risk of CV events and/or mortality (all-cause or CV mortality) in patients with CKD G3-G5.[18] FGF-23 has also been associated with increased mortality and CV events in individuals with CKD. The incidence of calciphylaxis, or rapid calcification of subcutaneous tissue, in patients with advanced kidney disease has increased over the past decade and has been associated with CKD-MBD, an elevated calcium times phosphorus product, and warfarin use.[17,19] Warfarin inhibits the matrix Gla protein, which is a vitamin-K-dependent protein that prevents calcium deposition in arteries, and may therefore promote vascular calcification in individuals at risk.[20] The decision to initiate warfarin therapy in patients with advanced kidney disease with a clinical indication (eg, atrial fibrillation) should take into account this additional risk of calcifications. Intake of calcium from calcium-based binders may also contribute to coronary artery calcification. These data underscore the need to consider all the consequences of elevated PTH, calcium, and phosphorus, not just their effects on bone.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Anemia and CKD-MBD

Signs and Symptoms

- Anemia: Fatigue, weakness, dizziness, headache, shortness of breath, mental confusion, cold intolerance, cold hands and feet, tingling in the extremities, chest pain, pale skin, irregular heartbeat.
- CKD-MBD: *Clinical presentation varies depending on the prevailing metabolic abnormality and characteristic bone disease (see Chapter 69, Calcium and Phosphorus Homeostasis).

Laboratory Tests

- Anemia: Decreased Hb/hematocrit (Hct), transferrin saturation (TSat), and/or ferritin (iron deficiency; note: ferritin may be increased due to inflammatory conditions), may be hemoccult-positive if GI bleeding present. Increased hepcidin.
- CKD-MBD: Decreased vitamin D levels, albumin, and calcium (in early stages of CKD). Increased: phosphorus, PTH, FGF-23, and calcium (more likely in CKD G5 and ESKD).

Diagnostic Considerations for Anemia of Chronic Kidney Disease

Since individuals with anemia of CKD may be asymptomatic, laboratory evaluation is commonly the initial approach to diagnosing anemia of CKD. According to the KDIGO guidelines, Hb concentrations should be measured annually in CKD 3, biannually in CKD 4-5, and at least every 3 months in CKD 5D patients.[14] The diagnosis of anemia is made and further workup of anemia is required when the Hb is less than 13 g/dL (130 g/L; 8.07 mmol/L) for adult males and less than 12 g/dL (120 g/L; 7.45 mmol/L) for adult females. As iron deficiency is the primary cause of resistance to treatment of anemia with ESAs, assessment of the iron status is necessary. The TSat provides information on iron immediately available for use in the bone marrow for red blood cell production and the serum ferritin is in indirect measure of storage iron. The TSat is calculated as follows: (serum iron/total iron-binding capacity [TIBC]) × 100. Transferrin is the carrier protein for iron and may be affected by nutritional status. Serum ferritin is an indirect measure of storage iron and an acute-phase reactant, meaning it may be elevated under certain inflammatory conditions and give a false indication of storage iron. Patients may be diagnosed with *absolute iron deficiency* when both circulating iron and stored iron are low (low TSat and ferritin). In CKD patients absolute iron deficiency has been defined as a TSat <20% (0.20) and a ferritin of <100 ng/mL (µg/L; 225 pmol/L) in ND-CKD patients and <200 ng/mL (µg/L; 449 pmol/L) in HD patients.[7] The term *functional iron deficiency* describes a situation when the TSat is low, but the serum ferritin is not considered low (TSat <20% [0.20], ferritin >100 and 200 ng/mL [µg/L; 225 and 449 pmol/L] for ND-CKD and HD patients, respectively). In this situation, iron is not released rapidly enough to satisfy the demands for erythropoiesis and further evaluation is warranted. While there is some controversy regarding the reliability of these definitions, particularly for functional iron deficiency, they do provide a working definition used in clinical practice. The KDIGO guideline for anemia does suggest TSat and serum ferritin thresholds that warrant iron supplementation (Table 63-2).[14]

TABLE 63-2

KDIGO Recommendations for Initiation of Erythropoiesis Stimulating Agents and Iron in Adults with Anemia of Chronic Kidney Disease

	ND-CKD	ESKD
ESA initiation	If Hb <10 g/dL (100 g/L; 6.21 mmol/L). Consider rate of fall of Hb, prior response to iron, risk of needing a transfusion, risk of ESA therapy, and presence of anemia symptoms before initiating an ESA. [2C] Do not initiate if Hb ≥10 g/dL (100 g/L; 6.21 mmol/L). [2D]	Use ESAs to avoid drop in Hb to <9 g/dL (90 g/L; 5.59 mmol/L) by starting an ESA when Hb is between 9 and 10 g/dL (90 and 100 g/L; 5.59 and 6.21 mmol/L). [2B]
Hb level	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]	Do not use ESAs to *intentionally* increase Hb above 13 g/dL (130 g/L, 8.07 mmol/L). [1A] Do not use ESAs to maintain Hb above 11.5 g/dL (115 g/L; 7.14 mmol/L). [2C]
Iron initiation[a]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (µg/L; 1,120 pmol/L). [2C]	If TSat is ≤30% (0.30) and ferritin is ≤500 ng/mL (µg/L; 1,120 pmol/L). [2C]

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; ESKD, end-stage kidney disease; Hb, hemoglobin; ND-CKD, non-dialysis CKD patients; QOL, quality of life; TSat, transferrin saturation.

See Chapter 62 for definitions of evidence grading in brackets.

[a]If TSat and serum ferritin are below suggested levels, consider iron supplementation if goal is to increase Hb and/or decrease ESA dose. *Note*: Serum ferritin is an acute-phase reactant-use clinical judgment when above 500 ng/mL (µg/L; 1120 pmol/L).

Data from Reference 14.

Additional workup should be done to evaluate other causes of anemia such as blood loss, deficiencies in vitamin B_{12} or folate, or other disease states that contribute to anemia, including human immunodeficiency virus infection and malignancies (see Chapter 122). Red blood cell indices (mean corpuscular volume, mean corpuscular Hb concentration), white blood cell count, differential and platelet count, and absolute reticulocyte count should also be assessed. A stool guaiac test should be performed to rule out GI bleeding. Measurement of serum erythropoietin concentrations is not generally useful since levels may fall into what is considered a “normal” range but are insufficient relative to the degree of decline in Hb.

Diagnostic Considerations for Chronic Kidney Disease–Related Mineral and Bone Disorder

Symptoms of CKD-MBD are often not evident until significant skeletal damage has developed; consequently, prevention is the key to minimize the risk of long-term complications. When signs and symptoms such as bone pain and skeletal fractures are evident, the disease is not easily amenable to treatment. Thus, the identification of biochemical or imaging abnormalities which typically precede clinical manifestations is an essential component of patient evaluation. The biochemical abnormalities of CKD-MBD that are commonly present in patients with CKD include alterations in serum phosphorus, calcium, PTH, 25(OH)D (D represents either D2 or D3), and $1,25(OH)_2D_3$ or calcitriol. Because of deficiency in the vitamin D precursor, 25(OH)D, is common and has been associated with negative outcomes in the CKD population, measurement of 25(OH)D levels in patients with CKD 3-5D is suggested.[17] The assay methods for 25(OH)D are not standardized, which creates a challenge regarding the clinical implications of abnormal values and limits its value as an indicator of therapeutic response.[21] Current monitoring recommendations and goals of therapy are covered in the “Treatment of CKD-MBD” section.

In addition to evaluating biochemical indices that define CKD-MBD, evaluation of bone architecture may be desirable. The gold standard test for diagnosing bone manifestations of CKD-MBD is a bone biopsy for histologic analysis; however, this is an invasive test that is not easily performed.

KDIGO guidelines recommend bone biopsy only in patients in whom the etiology of clinical symptoms and biochemical abnormalities is not clear and the results may lead to changes in therapy.[17] This includes patients experiencing unexplained fractures, persistent hypercalcemia, osteomalacia, an atypical response to standard therapies for elevated PTH, or progressive decreases in bone mineral density despite therapy. Bone biopsy findings are described on the basis of turnover rate, mineralization, and volume. Bone mineral density testing is recommended in patients with CKD G3-G5 and ESKD with evidence of CKD-MBD and/or risk factors for osteoporosis.[17] CKD-MBD is also highly associated with vascular and soft-tissue calcifications, known risk factors for mortality; therefore, diagnostic testing for calcifications should be considered in the evaluation for CKD-MBD.

TREATMENT OF SECONDARY COMPLICATIONS

General Approach to Treatment of CKD Complications

4 Management of complications of CKD should be based on the KDIGO consensus guidelines which are based on evidence, when available, and expert recommendations. There are guidelines provided by the Kidney Disease Outcome Quality Initiative (KDOQI) for many of the associated complications; however, this chapter emphasizes KDIGO guidelines, which are international guidelines and, in most cases, based on data or expert opinion. Chapter 62 includes a guide to the grading and strength of recommendations used in these guidelines.

5 An interdisciplinary approach to care should emphasize patient-centered care and at minimum include a team of nephrologists, nurses, dietitians, pharmacists, and social workers. This team approach puts the patient at the center and includes individuals trained to address many of the complex secondary complications of CKD and provide patient education about CKD, the associated complications, and their management. Treatment of secondary complications of CKD requires a number of pharmacologic intervention, thus adding to the number of medications required for patients with advanced CKD. Pharmacists are readily accessible medication experts equip to address medication-related problems and provide comprehensive medication management.

Anemia

Desired Outcome

The desired outcomes of anemia management are to safely achieve target Hb levels that increase oxygen-carrying capacity to decrease signs and symptoms of anemia and reduce the need for blood transfusions. Hb is the preferred monitoring parameter for red blood cell production because, unlike Hct, its concentration is not affected by blood storage conditions and instrumentation used for analysis. Initiation of iron or ESA therapy is guided by the patient's Hb, TSat, and ferritin (Table 63-2).[14] The risk of mortality and CV events is higher in CKD patients treated to higher Hb target values with an ESA. There are discrepancies, however, in the FDA-approved labeling for ESAs and the KDIGO anemia guidelines in terms of target Hb, with more conservative Hb of 10 to 11 g/dL (100-110 g/L; 621-683 mmol/L) recommended by the FDA for individuals with ESKD.[14]

Despite associations of development of left ventricular hypertrophy (LVH) with worsening anemia, there are no prospective studies demonstrating that early and aggressive treatment improves CV end points or reduces LVH in CKD patients. Improvements in the quality of life are not universally observed with increases in Hb and such perceived improvements must be weighed against reported risks associated with using ESAs in the CKD population.[22]

Target Hemoglobin and Use of Erythropoiesis Stimulating Agents

The target range for Hb in the CKD population has been a topic of much debate. Although the benefits of achieving a normal or near normal Hb seemed rational when ESAs became available in the late 1980s, the Normal Hematocrit Cardiac Trial (NHCT),[23,24] the Correction of Hb and Outcomes in Renal Insufficiency (CHOIR),[25] and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin-Beta (CREATE)[26] trials later proved otherwise, and the suggested target Hb at the time of those trials of 11 to 12 g/dL (110-120 g/L; 6.83-7.45 mmol/L) was subsequently lowered. Several FDA advisories have been released and changes were made to the precautions, black box warning, and dosing sections of ESA product labeling promoting more conservative use of ESAs.[27] The current labeling for all ESAs warns that dosing ESAs to target Hb levels greater than 11 g/dL (110 g/L; 6.83 mmol/L) for CKD patients increases the risk for death, serious CV reactions, and stroke. Practitioners are advised to consider ESAs in patients with CKD only when the Hb is below 10 g/dL (100 g/L; 6.21 mmol/L) and to individualize therapy to use the lowest ESA dose necessary to decrease the need for red blood cell transfusions.

Of concern is the fact that CHOIR demonstrated that targeting Hb levels above 11 g/dL (110 g/L; 6.83 mmol/L) with ESA therapy in individuals with CKD not requiring dialysis resulted in increased risk of mortality and CV events compared with patients maintained in a lower Hb range (trial was terminated early).[25] CREATE demonstrated no benefit of targeting a higher Hb target (13-15 g/dL [130-150 g/L; 8.07-9.31 mmol/L]) to reduce CV events in the ND-CKD patients.[26] An increased risk of all-cause mortality with ESA treatment was also reported in a meta-analysis of nine randomized controlled trials that included over 5,100 CKD patients treated to Hb targets in the range of 12 to 16 g/dL (120-160 g/L; 7.45-9.93 mmol/L).[28] There was also a higher risk of dialysis access thrombosis and uncontrolled blood pressure in the higher Hb groups. Results from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) also failed to support a higher Hb.[29] In addition, there was also an almost twofold increase in the risk of stroke (5% in the treatment group vs 2.6% in the placebo group), a finding that was not associated with baseline characteristics of the patients or other potential risk factors. Those patients with a history of cancer in the higher Hb group also had a higher risk of death.

The overall negative CV outcomes observed with higher Hb targets in the randomized trials have prompted much discussion about the potential causes, including not only ESA dose and Hb target, but also the rate of rise in Hb and the variability in Hb over time (eg, degree of fluctuation in Hb). Individuals in the CHOIR study who were able to achieve the target Hb did not have worse outcomes. Further analysis of the NHCT data also showed a reduction in mortality by 60% for those individuals who responded to epoetin therapy compared with nonresponders.[24] Resistance to ESAs was associated with higher 1-year mortality and hospitalization for CV events.[30] Such findings have led to discussion of whether hyporesponsiveness to ESAs due to other conditions such as inflammation may explain the higher event rates in this group of individuals.

Nonpharmacologic Therapy

Nonpharmacologic therapy for anemia of CKD includes maintaining adequate dietary intake of iron as well as folate and B_{12}. A relatively small amount of dietary iron, approximately 1 to 2 mg, is absorbed each day, primarily in the duodenum. While oral intake or iron should be encouraged, iron from dietary sources alone is insufficient to meet the increased iron requirements from initiation of ESA therapy.

Pharmacologic Therapy

6 Pharmacologic therapy for anemia of CKD includes iron supplementation to prevent and correct iron deficiency and ESAs to correct erythropoietin deficiency. Iron supplementation is first-line therapy for anemia of CKD if iron deficiency is present, and for some patients, the target Hb may be achieved with iron therapy alone. For most individuals with advanced CKD, however, combined therapy with iron and an ESA will be necessary to achieve the target Hb.

The HIF prolyl hydroxylase inhibitors (HIF-PHIs) (daprodustat, roxadustat, vadadustat) have been considered for approval by the Food and Drug Administration Currently, only daprodustat has received a favorable review in terms of efficacy and safety in the dialysis population. These HIF-PHIs are orally administered medications that have been studied in patients with ND-CKD and ESKD with positive results in terms of improving Hb and decreasing hepcidin levels to promote better iron distribution and utilization, without raising erythropoietin levels to levels achieved with exogenous ESA administration.[31] Agents within this drug class have been approved outside the United States and are part of the pharmacologic regimen for the management of anemia of CKD.

Iron Supplementation

Iron formulations are available for administration orally, intravenously, or through the dialysate used for hemodialysis. Iron supplements provide the elemental iron required for production of Hb and its subsequent incorporation in red blood cells, the net result of which is an increase in the transportation of oxygen to tissues. Iron supplementation is necessary to treat *absolute iron deficiency*, but may also be warranted in individuals with a TSat less than 30% (0.30) and a ferritin less than 500 ng/mL (µg/L; 1,120 pmol/L) in whom an increase in Hb or a decrease in ESA dose is desired (KDIGO suggestion).[14] Patients with *functional iron deficiency* may also benefit from iron supplementation. The optimal upper limit for these iron indices is not clearly defined and clinicians must balance achieving adequate iron for erythropoiesis with safety in terms of preventing adverse consequences such as iron overload and concerns with nontransferrin (unbound) iron.

The preferred route of administration depends on CKD stage, severity of iron deficiency, tolerability of and prior response to oral iron, history of adverse reactions to IV iron, availability of IV access, and cost (see the "Therapeutic Options" section). KDIGO recommends either oral or IV iron

administration in non-HD patients (eg, CKD stage G3 or higher) and IV supplementation for patients with ESKD.[14] The National Institute for Health Care Excellence (NICE) guidelines suggest a trial of oral iron (for up to 3 months) in ND-CKD patients not receiving an ESA and IV iron for patients treated with and ESA and/or on HD.[32] Oral iron supplementation is more convenient for ND-CKD patients since they do not have regular IV access; however, at some point they are likely to require IV iron supplementation to correct absolute iron deficiency, especially if they are receiving an ESA. If oral therapy is initiated, a 1- to 3-month trial is recommended to assess response. In patients with CKD on hemodialysis, GI absorption of iron is often inadequate to meet the increase in iron demand from ESA therapy and chronic blood loss, due largely to the effects of hepcidin on GI absorption. Thus, the IV route is preferred for almost all HD patients.[14] IV administration is also recommended in the peritoneal dialysis (PD) population, although the desire to preserve potential future venous access sites for HD (if needed) must be considered. Parenteral iron improves the responsiveness to ESA therapy and, thus, lower ESA doses can be used to maintain the target Hb in HD patients.[14] In the FIND-CKD trial, 624 ND- CKD patients were randomized to IV ferric carboxymaltose administered at high dose (1,000 mg every 4 weeks) to target a ferritin of 400 to 600 ng/mL (µg/L; 899-1348 pmol/L), low dose (200 mg every 4 weeks) to target a ferritin of 100 to 200 ng/mL (µg/L; 225-449 pmol/L), or oral iron administered as 200 mg/day. After 56 weeks, the high ferritin IV iron group had better outcomes in terms of the increase in mean Hb at 12 months and time to achieve that level, but no differences in adverse events. Iron administration in patients with functional iron deficiency (ie, low TSat, high serum ferritin) should be decided on an individual basis. A trial of IV iron therapy may be warranted if the Hb is less than desired despite high-dose ESA therapy as long as potential risks of IV therapy are considered (see the "Adverse Effects" section).

Therapeutic Options

Multiple oral and IV products are marketed in the United States. Oral iron preparations include ferrous and ferric salts (ferrous sulfate, ferrous fumarate, ferrous gluconate, ferric citrate, and ferric maltol), polysaccharide iron complex, and carbonyl iron. These forms of iron differ in terms of the amount of elemental iron (Table 63-3). A heme iron polypeptide formulation is also available and contains 12 mg of elemental iron. Numerous nonprescription products that contain ferrous salts and iron polysaccharide are available. Ferric maltol is a newer agent available by prescription containing 100% elemental iron that is approved for iron deficiency anemia in adults. Ferric citrate was originally developed as a phosphate binding agent but was subsequently shown to improve iron status and Hb levels also, leading to its approval for treatment of iron-deficiency anemia in ND-CKD patients.[33]

TABLE 63-3

Oral Iron Agents

Preparation	Brand Names[a]	[c]% Elemental Iron	Commonly Rx'd
			Unit Size in mg (Amount elemental iron)
Carbonyl iron	Feosol, Ferralet (combo with ferrous gluconate, docusate)	100	45 (45)
Ferric citrate[b]	Auryxia	21	1,000 (210)
Ferric maltol[b]	Accufer	100	30 (30)
Ferrous fumarate	Femiron, Feostat	33	200 (66)
Ferrous gluconate	Simron, Fergon	12	325 (38)
Ferrous sulfate	Feosol, Fer-In-Sol	20	325 (65)
Iron Polysaccharide	Niferex, Nu-Iron	100	150 (150)

[a]Not all inclusive for over-the-counter medications (ie, ferrous salts).

[b]Available by prescription only.

[c]Generally target a dose of 200 mg elemental iron per day. Ferric citrate and ferric maltol approved at different doses [ferric citrate - 210 mg (one tablet) three times daily; ferric maltol - 30 mg (one capsule) twice daily]

Iron is absorbed from the GI tract via the divalent metal transporter 1 in the duodenum and upper jejunum where approximately 10% of orally administered iron is absorbed. Ferroportin transports iron across the mucosal cell to the blood where it is bound to transferrin. Immediate release oral iron agents are preferred over enteric coated and slow or sustained release products, which are absorbed more distally in the GI tract and not as readily absorbed. Absorption of iron is decreased by food and achlorhydria. Some oral iron formulations also include ascorbic acid to enhance iron absorption, although data to support this practice are lacking. The role of hepcidin to decrease GI absorption is also a significant factor that influences iron regulation and a reason that oral therapy may be inadequate to meet iron needs, particularly in HD patients.

Soluble ferric pyrophosphate citrate (Triferic) is an iron compound approved for iron replacement in patients with ESKD on HD and may be administered via the dialysate during HD or intravenously using the IV formulation (Triferic AVNU). When administered in the dialysate, this agent crosses to the blood side of the dialyzer by diffusion to allow for continuous iron administration during the procedure. Ferric pyrophosphate citrate is a mixed-ligand iron complex with iron bound to pyrophosphate and citrate. Once in the systemic circulation ferric pyrophosphate binds directly to transferrin, bypassing the reticuloendothelial system, and is delivered to the bone marrow for use in red blood cell production. Studies to date have shown an increase in Hb concentration and a reduction in ESA dose and IV iron requirements, but no significant increase in ferritin or in nontransferrin bound iron.[34,35] These findings are important when considering the potential adverse effects associated with iron accumulation and free (unbound) iron.

Most IV iron preparations are colloids that consist of an iron-containing core that is surrounded by a carbohydrate shell to stabilize the iron complex. Available agents differ in the size of the core and the composition of the surrounding carbohydrate. Such differences affect the rate of dissociation of iron from the complex, the rate of distribution, and the maximum tolerated dose and rate of infusion. The IV iron products that are currently available

in the United States are shown in Table 63-4.

TABLE 63-4

Intravenous Iron Agents

Iron Compounds	Brand Names	Molecular Weight (Daltons)	FDA-Approved Indications	FDA-Approved Dosing[a,b]
Ferric carboxymaltose	Injectafer	150,000	Adult patients with intolerance to oral iron or who have had an unsatisfactory response to oral iron and in adult patients with CKD not on dialysis	Give 2 doses separated by at least 7 days of 750 mg per dose (if body weight is ≥50 kg) or 15 mg/kg per dose (if body weight is <50 kg) not to exceed 1,500 mg per course. Give either IV push (100 mg/min) or diluted in not more than 250 mL of 0.9 NaCl as an infusion over at least 15 minutes
Ferric derisomaltose	Monoferric	155,000	Treatment of iron deficiency anemia in adults with ND-CKD or who have intolerance to oral iron or unsatisfactory response to oral iron	If weight ≥50 kg: 1,000 mg as a single dose If weight <50 kg administer 20 mg/kg actual body weight as a single dose
Ferric pyrophosphate citrate	Triferic AVNU	1,313	Iron replacement to maintain Hb in adult patients with ESKD on hemodialysis	6.75 mg iron over 3 to 4 hours at each HD session via pre-dialyzer infusion line, post-dialyzer infusion line, or a separate connection to the venous blood line
	Triferic			Add the appropriate ampule or powder packet* to the bicarbonate concentrate solution to achieve a final concentration of ferric pyrophosphate citrate of 110 µg/L *add one 5 mL ampule to 2.5 gallons (9.5 L) of bicarbonate concentrate or one 50 mL ampule to 25 gallons (95 L) of bicarbonate or one packet of powder to each 25 gallons ampule (95 L)
Ferumoxytol	Feraheme	750,000	Adult patients with iron-deficiency anemia associated with chronic kidney disease	510 mg (17 mL) as a single dose, followed by a second 510 mg dose 3-8 days after the initial dose. Dilute in 50-200 mL of 0.9% NaCl or 5% dextrose and administer as an IV infusion over 15 minutes
Iron dextran	INFeD	96,000	Patients with iron deficiency in whom oral iron is unsatisfactory or impossible	100 mg over 2 minutes (25-mg test dose required) Note: Equation provided by manufacturer to calculate dose based on desired Hb
Iron sucrose	Venofer	43,000	Adult and pediatric ESKD patients on HD age 2 years and older	Adult: 100 mg over 2-5 minutes or 100 mg in maximum of 100 mL of 0.9% NaCl over 15 minutes per consecutive HD session Pediatric: 0.5 mg/kg not to exceed 100 mg per dose over 5 minutes or diluted in 25 mL of 0.9% NaCl administered over 5-60 minutes (give dose every 2 weeks for 12 weeks)

			Adult and pediatric ND-CKD patients age 2 years and older	Adult: 200 mg over 2-5 minutes on five different occasions within 14-day period. There is limited experience with administration of 500 mg diluted in a maximum of 250 mL of 0.9% NaCl over 3.5-4 hours on days 1 and 14 Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)
			Adult and pediatric ESKD patients on PD, age 2 years and older	Adult: give 3 divided doses within 28 days as 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute in a maximum of 250 mL of 0.9% NaCl Pediatric: see pediatric dosing for CKD 5HD (give dose every 4 weeks for 12 weeks)
Sodium ferric gluconate	Ferrlecit	350,000	Adult and pediatric ESKD patients on HD age 6 years and older receiving ESA therapy	Adult: 125 mg over 10 minutes or 125 mg in 100 mL of 0.9% NaCl over 60 minutes Pediatric: 1.5 mg/kg in 25 mL of 0.9% NaCl over 60 minutes; maximum dose 125 mg per dose

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; ESKD, end-stage kidney disease; HD, hemodialysis; ND-CKD, non-dialysis CKD patients.

[a]Monitor for 30 minutes following an infusion; KDIGO guidelines recommend monitoring for 60 minutes (1B recommendation for iron dextran, 2C recommendation for non-dextran products).

[b]With the exception of ferric carboxymaltose, ferric derisomaltose, and ferumoxytol, small doses (eg, 25-150 mg/wk) are generally used for maintenance regimens. Larger doses (eg, 1 g) should be administered in divided doses. The IV form of ferric pyrophosphate citrate (Triferic AVNU) is administered in smaller increments (6.75 mg)

Adverse Effects

Adverse effects of oral iron are primarily GI in nature and include constipation, nausea, and abdominal cramping (see Chapter 122). These adverse effects are more likely as the dose is escalated. These unfavorable effects often discourage patients from taking these medications on a chronic basis. Some of these GI side effects can be minimized if oral iron products are taken with food; however, food may decrease absorption of oral iron.

Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions, in particular hypotension, can be minimized by decreasing the dose or rate of infusion of iron. The most concerning potential consequence of IV iron administration is anaphylaxis. Serious reactions to iron dextran including respiratory complications and CV collapse have been reported in approximately 0.6% to 0.7% of patients.[14] Such reactions are believed to be partly a response to antibody formation to the dextran component. Adverse reactions were reported more frequently with the brand product Dexferrum (no longer available) compared with INFeD.[14] Iron dextran carries a black box warning of the risk of anaphylactic-type reactions, including fatalities, and a 25-mg test dose is required. An analysis of anaphylaxis risk in patients newly exposed to IV iron products (including dextran, gluconate, sucrose, or ferumoxytol) reported the highest risk for iron dextran and the lowest risk with iron sucrose.[36]

The non-dextran IV iron formulations have a better safety record than either of the iron dextran products. The labeling for these formulations also includes a warning of the risk of hypersensitivity reactions. Following the approval of ferumoxytol in 2009, there were 79 cases of anaphylactic

reactions, of which 18 were fatal.[37] Almost half of the cases occurred with the first dose and approximately 75% occurred during the infusion or within 5 minutes of completion. In 2015, the FDA required a black box warning for ferumoxytol noting that fatal and serious hypersensitivity reactions including anaphylaxis have occurred and that the risks and benefits should be considered in patients with a history of multiple drug allergies. Ferumoxytol should not be administered IV push, but should be diluted and administered as an IV infusion (see Table 63-4). As a superparamagnetic oxide, ferumoxytol may alter the diagnostic ability of magnetic resonance imaging studies for up to 3 months after administration; therefore, they should be done prior to administration of ferumoxytol whenever possible.

Long-term administration of IV iron also introduces a risk of iron overload. Deposition of excess iron may affect several organ systems, leading to hepatic, pancreatic, and cardiac dysfunction. Bone marrow biopsy provides the most definitive diagnosis of iron overload, but because it is an extremely invasive procedure, it is not widely employed in most clinical settings. Maintaining target serum ferritin and TSat values is the most reasonable approach to minimize the risk of iron toxicity. The challenge is in defining what should be the upper limit, particularly for serum ferritin, which may be elevated in inflammatory conditions and not reflective of true iron stores in such situations. If symptomatic overload does occur, iron chelating agents such as deferoxamine (Desferal), deferiprone (Ferriprox), deferasirox (Exjade), or phlebotomy may be necessary.

More conservative use of ESAs has led to an increase in iron supplementation. This has raised some concerns regarding the potential detrimental effects of increased iron exposure and higher TSat and ferritin targets on patient outcomes (eg, infection, mortality, hospitalizations). Specific concerns relate to the ability of iron to promote infection since iron is essential for infectious microorganisms, increased risk of oxidative stress, and subsequent cardiovascular complications, as well as the concerns of other effects of non-transferrin bound iron (unbound/free iron). Data from clinical trials do not confirm unequivocally that exposure to IV iron in CKD patients treated with ESA therapy increases patient morbidity or mortality.[7,38-42]

A large randomized controlled trial in the United Kingdom (PIVOTAL trial) evaluated the safety of high-dose IV iron (400 mg/month) administered proactively (with the upper TSat limit 40% [0.40] and ferritin of 700 ng/mL [µg/L; 1,573 pmol/L]) and low-dose IV iron (0-400 mg monthly) administered reactively (with a TSat <20% [0.20] or a ferritin <200 ng/mL [µg/L; 449 pmol/L] prompting the need for IV iron administration) in 2,141 dialysis patients over a median of 2 years.[38] There were significantly fewer deaths and nonfatal CV events (nonfatal MI, stroke, hospitalization for heart failure) in the high-dose group compared to the low-dose group and a lower requirement for ESAs and transfusions. The high-dose and low-dose IV iron groups exhibited identical infection rates.[42] This is the most robust evidence to date that IV iron at this dose level and prespecified iron targets is safe in HD patients. Caution is recommended with the use of IV iron doses higher than those used in the PIVOTAL trial as observational data have suggested associations with increased risk of mortality and infection. Although more data are needed to draw conclusions, the general consensus is that administration of IV iron in the setting of an active infection is not recommended.[7] The benefits of correcting iron deficiency in patients with CKD should also be considered in the clinical decision process.

Drug Interactions

Drug interactions with oral iron are common. Iron absorption is decreased by other elements (eg, calcium in calcium-containing phosphate binders), medications that increase the pH of the GI tract such as proton pump inhibitors and H_2-antagonists, and antibiotics including doxycycline and tetracycline. Iron also decreases absorption of other drugs such as antibiotics (fluoroquinolones, doxycycline).

If oral therapy is initiated, the suggested dose is 200 mg of elemental iron per day for most available agents. The approved dose of ferric maltol is 30 mg twice daily. The recommended dose of ferric citrate in ND- CKD patients is 210 mg three times daily. With numerous oral agents to choose from, the best option is one that provides adequate elemental iron with the fewest number of dosage units required per day and the lowest incidence of adverse effects. Strategies to improve absorption and potentially minimize adverse GI events have been evaluated in non-CKD patients and include single-dose administration of ferrous sulfate on alternate days, which resulted in a decrease in hepcidin and improved iron absorption, although such data in CKD patients are not available.[43] KDIGO guidelines suggest a 1- to 3-month trial of oral therapy in the non-HD CKD population prior to initiating IV therapy.[14]

For the HD population, IV therapy is preferred with administration of a 1-g course of IV iron (in divided doses) historically used to replete patients with an absolute iron deficiency. The amount per dose and rate at which to administer IV iron depends on the product (see Table 63-4). Typical repletion dosing regimens for IV iron are 100 mg as iron sucrose over 10 dialysis sessions or 125 mg of sodium ferric gluconate over eight dialysis sessions to provide a total of 1 g. As a general practice, if IV iron doses higher than those currently approved are needed, they should be infused over a longer period of time (eg, at least 2-4 hours) due to the risk of hypersensitivity reactions, hypotension, dizziness, and nausea. The newer agents, ferumoxytol,

ferric carboxymaltose, and ferric derisomaltose differ in terms of how rapidly iron is released from the compound, which allows for higher single doses to be administered compared to the other IV iron agents (Table 63-4). Ferric pyrophosphate citrate when given IV is approved at smaller doses of 6.75 mg given over 2 to 4 hours during each HD session. When administered via the dialysate used for HD, the ampule or powder is added to the bicarbonate concentrate solution used for dialysis to achieve a final concentration of 110 µg/L.

Without ongoing iron supplementation, many patients quickly become iron deficient. To prevent iron deficiency and the need for intermittent repletion doses, maintenance doses of IV iron should be administered in HD patients (eg, iron sucrose 25-100 mg/wk; sodium ferric gluconate 62.5-125 mg/wk).[14] There are many different maintenance dosing protocols in clinical practice for CKD patients and some controversy as to the maximum monthly doses given safety concerns (see the "Adverse Events" section). The main consideration is to provide enough iron to help achieve goal hemoglobin levels and to reduce the need for ESAs and transfusions, while minimizing risks of IV iron.

Administration of a 25-mg test dose is required for all iron dextran products. This test dose should be administered over at least 30 seconds. It is recommended that patients be observed for at least 1 hour before administering the remainder of the dose. For this reason, the non-dextran agents are predominantly used in the CKD population. Regardless of which IV iron agent is used, all patients should be monitored for signs and symptoms of hypersensitivity for at least 30 minutes following completion of a dose. KDIGO clinical practice guidelines suggest monitoring patients for at least 60 minutes following administration of IV iron; a 1B recommendation for iron dextran products and a 2C recommendation for non-dextran formulations.[14] These agents should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

Erythropoiesis-Stimulating Agent Therapy

Since FDA approval of epoetin-alfa in 1989, ESA therapy has become an integral part of the care for patients with CKD. ESAs available in the United States are listed in Table 63-5. The biosimilar epoetin-alfa epbx is approved in the United States. As a biosimilar, this agent has the same indications as the biological drug, epoetin-alfa.

TABLE 63-5

Erythropoiesis-Stimulating Agents in Chronic Kidney Disease

Drug Name	Brand Name(s)	Starting Dose	Route of Administration	Half-Life (Hours)
Epoetin-alfa	Epogen, Procrit	Adults: 50-100 units/kg three times per week Pediatrics: 50 units/kg three times per week	IV or SUBQ	8.5 (IV) 24 (SUBQ)
Epoetin-alfa-epbx	Retacrit	See epoetin-alfa information		
Darbepoetin alfa	Aranesp	Adults: ND-CKD: 0.45 µg/kg once every 4 weeks ESKD: 0.45 µg/kg once per week or 0.75 µg/kg every 2 weeks Pediatrics: 0.45 µg/kg once weekly; may give 0.75 µg/kg once every 2 weeks in ND-CKD patients	IV or SUBQ	25 (IV) 48 (SUBQ)
Methoxy PEG-epoetin-beta	Mircera	All adult CKD patients: 0.6 µg/kg every 2 weeks; Once Hb stabilizes, double the dose and administer monthly (eg, if administering 0.6 µg/kg every 2 weeks, give 1.2 µg/kg every month)	IV or SUBQ	134 (IV) 139 (SUBQ)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; ND-CKD, non-dialysis CKD patients; PEG, polyethylene glycol; SUBQ, subcutaneous.

Pharmacology and Mechanism of Action

Epoetin-alfa is a glycoprotein manufactured by recombinant DNA technology that has the same amino acid sequence as endogenous erythropoietin. Darbepoetin alfa has two additional *N*-linked carbohydrate chains that decrease the affinity for the erythropoietin receptor, but yield a longer duration of activity compared with erythropoietin. Methoxy PEG-epoetin-beta was created by the addition of an amide bond between the N-terminal or ε-amino group of epoetin-beta and methoxy polyethylene glycol butanoic acid. The compound, which is referred to as a continuous erythropoietin receptor activator (CERA), has a much longer half-life than the other ESAs. All ESAs have the same biologic activity as endogenous erythropoietin in that they bind to and activate the erythropoietin receptor to stimulate erythropoiesis.

Pharmacokinetics and Pharmacodynamics

All available ESAs may be administered via either the IV or the subcutaneous (SUBQ) route. Although bioavailability is less with SUBQ than with IV administration, the prolonged absorption phase leads to an extended half-life (see Table 63-5). Thus, the same target Hb can be achieved and maintained at SUBQ epoetin doses 15% to 30% lower than IV doses.[14] The prolonged half-lives of darbepoetin-alfa and methoxy PEG-epoetin-beta offer the advantage of less-frequent dosing. This is of particular benefit for individuals with CKD who are not yet receiving dialysis and those receiving PD since these patients are not in a clinical setting as frequently as HD patients and do not have regular IV access.

The pharmacodynamic effect of ESAs is important to consider when evaluating response to therapy. With initiation of ESA therapy or a change in dose, the Hb may begin to rise as the result of demargination of reticulocytes; however, it takes approximately 10 days before erythrocyte progenitor cells mature and are released into the circulation. The Hb continues to increase until the life span of the cells stimulated by ESA therapy is reached (mean 2 months; range 1-4 months in patients with ESKD). At this point, a new steady state is achieved (ie, the rate at which red blood cells are being produced

equals the rate at which they are leaving the circulation). For this reason, evaluate the Hb response over several weeks and not make dosing changes too soon.

Efficacy

Patients will generally respond to ESA therapy in a dose-related fashion. The most common causes of resistance are iron deficiency, acute illness, inflammation, infection, chronic bleeding, aluminum toxicity, malnutrition, hyperparathyroidism, cancer, and chemotherapy.[14] Deficiencies in folate and vitamin B_{12} should also be considered as potential causes of resistance to ESA therapy, as both are essential for optimal erythropoiesis. Use of ACEIs and ARBs has also been associated with hyporesponsiveness to ESA therapy.[14]

Hypertension is the most common adverse event reported with ESAs and may be associated with the rate of rise in Hb.[10] Hypertensive encephalopathy has also been observed. According to FDA-approved product labeling, ESAs should not be used in those with uncontrolled blood pressure. Protocols established in some clinical settings recommend withholding ESA therapy if blood pressure is above a defined threshold; however, others advocate more judicious use of antihypertensive agents and dialysis to control blood pressure. Seizures have occurred in patients treated with ESAs, particularly within the first 90 days of starting therapy. Thrombosis of the HD vascular access site and other thromboembolic events were reported when ESAs were used to target Hb greater than 13 g/dL (130 g/L; 8.07 mmol/L).[44] The potential for these adverse effects calls for close monitoring of the rate of rise in Hb, changes in blood pressure, and neurologic symptoms following initiation of therapy or a change in ESA dose.

Antibody-associated pure red cell aplasia (PRCA), caused by induction of antibodies directed against the ESA molecule, was reported in the late 1990s and early 2000 and was primarily associated with subcutaneous administration of Eprex, an epoetin-alfa formulation manufactured outside the United States.[45] This reaction was potentially a result of organic compounds being formed when the stabilizing agent polysorbate was used in combination with uncoated rubber stoppers in the prefilled syringes. There have been few cases since changes in the packaging of this product were made; however, the cause of PRCA with this formulation has been disputed.[46] Of note, there have been reports of PRCA with methoxy PEG-epoetin-beta.[47] An evaluation for PRCA should be considered for patients receiving ESA therapy for more than 8 weeks who develop either a rapid decrease in Hb level (rate of 0.5-1 g/dL/wk [5-10 g/L/wk; 0.31-0.62 mmol/L/wk]) or require one to two blood transfusions per week, and have an absolute reticulocyte count of less than 10,000/µL (10×10^9/L) with a normal platelet and white blood cell count.[14] Discontinuation of ESA therapy is recommended if antibody-mediated PRCA develops because antibodies are cross-reactive and continued exposure may lead to anaphylactic reactions (a grade 1A recommendation).

ESAs have also been associated with a reduction in overall survival and increased risk of progression of certain tumor types among CKD patients (eg, head and neck). ESAs are not indicated in patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. These are important effects to consider when managing a CKD patient with an oncologic disorder.[48]

Drug-Drug Interactions

No significant drug interactions have been reported with the available ESAs.

Dosing and Administration

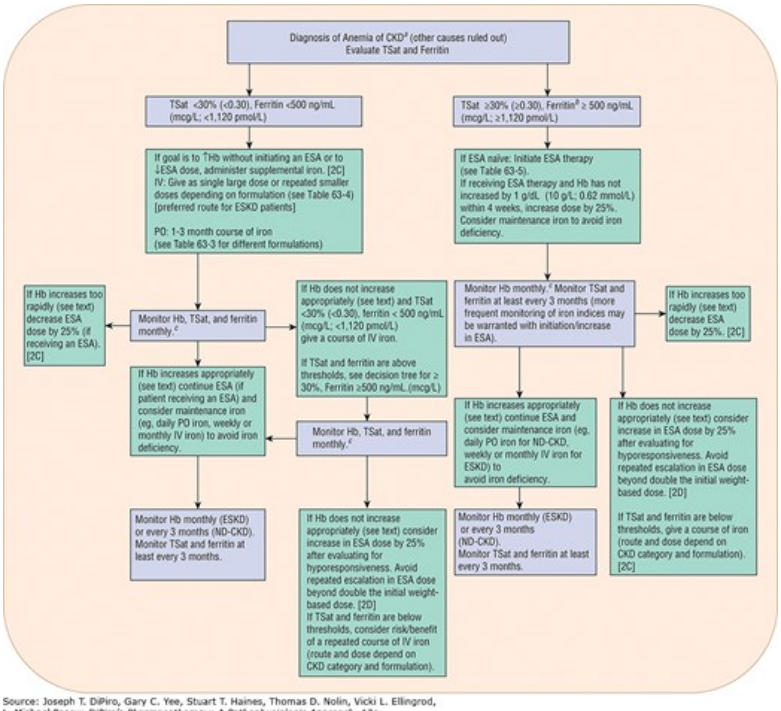
Recommended starting doses of ESA are listed in Table 63-5. Less-frequent dosing of epoetin-alfa (eg, every 1-2 weeks) is effective and may be preferred for ND-CKD patients since these individuals are seen in the outpatient clinical setting on a relatively infrequent basis. Subcutaneous dosing is also more convenient in this population and in PD patients who do not have regular IV access. Conversion tables for patients who are to be switched from epoetin-alfa (units/wk) to darbepoetin-alfa (µg/wk) are available in the labeling information for darbepoetin.[49] There is also a conversion chart for patients being converted from epoetin-alfa or darbepoetin-alfa to methoxy PEG-epoetin-beta.[47]

When starting an ESA, Hb levels should be monitored at least monthly (weekly may be preferred) until stable and then monthly thereafter. Dose adjustments should be made based on Hb response with a goal of avoiding an excessively quick rise or the achievement of values above the recommended target values. An acceptable rate of increase in Hb is 1 to 2 g/dL (10-20 g/L; 0.62-1.24 mmol/L) per month. As a general rule, ESA doses should not be increased more frequently than every 4 weeks, although decreases in dose may occur more frequently in response to a rapid rate of rise

in Hb. The dose should be reduced by at least 25% if the Hb increases by more than 1 g/dL (10 g/L; 0.62 mmol/L) in a 2-week period.[10] The dose should be reduced or temporarily discontinued if the Hb level approaches or exceeds 11 g/dL (110 g/L; 6.83 mmol/L) in dialysis patients or 10 g/dL (100 g/L; 6.21 mmol/L) in patients with CKD not requiring dialysis. KDIGO recommendations advocate a decrease in dose as opposed to withholding the ESA when a decrease in Hb concentration is desired (2C grade recommendation).[14] A 25% increase in dose may be considered if the Hb has not increased by 1 g/dL (10 g/L; 0.62 mmol/L) after 4 weeks of ESA treatment and if no causes of hyporesponsiveness to the ESA have been identified. For patients who do not respond adequately over a 12-week escalation period, an increase in ESA dose is unlikely to improve response and may increase risks. Initial hyporesponsiveness to ESAs should be considered when there is no increase in Hb from baseline after the first month of appropriate weight-based dosing. In this situation escalations in ESA dose beyond double the initial weight-based dose should be avoided (a grade 2D recommendation). Acquired ESA hyporesponsiveness may be suspected when patients previously on a stable ESA dose require two increases in ESA doses up to 50% beyond the previously utilized stable dose.[14] In this situation, repeat escalations in ESA dose beyond double the dose at which they had been stable should be avoided (a grade 2D recommendation). The lowest dose of ESA should be used to maintain an Hb level sufficient to reduce the need for red blood cell transfusions. Figure 63-4 provides an approach to management of anemia using ESAs and iron therapy in patients with CKD.

FIGURE 63-4

Algorithm for management of anemia of CKD in adults.[14,44] (CKD, chronic kidney disease; ESKD, end-stage kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, non-dialysis CKD patients; TSat, transferrin saturation.) Evidence grading in brackets. [a]See Table 63-2 and text for discussion of Hb levels. [b]Clinical judgment should be used to determine if iron supplementation should be continued when ferritin >500 ng/mL (µg/L; 1,120 pmol/L). [c]Weekly monitoring of Hb may be warranted. Wait at least 1 week after an IV dose of iron to measure TSat and ferritin.



Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

A key target for anemia management in CKD is the development of HIF-prolyl-hydroxylase (HIF-PH) inhibitors or HIF stabilizers that mimic the conditions of hypoxia to prevent the hydroxylation process. The HIF-PH inhibitors in development in the United States include roxadustat, daprodustat, and vadadustat.[11,50] Demonstrated benefits include improvement in hemoglobin levels and induction of physiologic blood levels of erythropoietin. These agents also decrease hepcidin, increase iron absorption, and improve functional iron deficiency. There is some concern that long-term use of these agents and sustained HIF activation may promote tumor progression due to the effects on vascular endothelial growth factor and angiogenesis. While there remains much to learn about HIF-PH inhibitors, these agents are likely to become an integral therapy for anemia

management in CKD. At the present time, only daprodustat has received a favorable review by the FDA for anemia of CKD in dialysis-dependent patients.

Transfusions and Adjunct Therapies

Red blood cell transfusions carry many risks and therefore should only be used in select situations, such as acute management of symptomatic anemia, following significant acute blood loss, and prior to surgical procedures that carry a high risk of blood loss, with the goal of preventing inadequate tissue oxygenation or cardiac failure. L-carnitine supplementation and vitamin C were previously suggested as adjunctive treatments of CKD anemia, but are not recommended because of the lack of evidence supporting improved anemia management with these therapies.[14]

Evaluation of Therapeutic Outcomes

Important therapeutic outcomes to monitor in patients with anemia of CKD include Hb, iron status, as well as the need for blood transfusions. Iron status should be assessed at least every 3 months in patients receiving a stable ESA regimen.[14] Iron status should be monitored more frequently (eg, every month) when initiating or increasing the ESA dose, following a course of IV iron, or when other factors put the patient at risk for iron loss (eg, bleeding). Hb levels should be monitored at least every 3 months in patients with ND-CKD or PD patients and at least monthly in HD patients. Hb should be monitored at least monthly in patients started on ESA therapy until the Hb is stable. Of note, FDA labelling for ESAs recommends weekly monitoring of Hb with initiation of therapy or a change in dose until the Hb is stable.[44,47,49]

MINERAL AND BONE DISORDER

Management of PTH, phosphorus, and calcium is important in preventing CKD-MBD and CV and extravascular calcifications. Patients with CKD-MBD usually require a combination of dietary intervention, phosphate-binding medications, vitamin D, and calcimimetic therapy (for ESKD patients) to achieve these goals.

Desired Outcome

7 The desired outcomes for management of CKD-MBD are to “normalize” the biochemical parameters and prevent bone manifestations, CV and extravascular calcifications, and the associated morbidity and mortality with both nonpharmacologic and pharmacologic interventions. At present, the 2017 KDIGO clinical practice guideline update for CKD-MBD is the most recent guideline clinicians use in their patient care decision-making process.[17]

The KDIGO-recommended targets for calcium, phosphorus, and PTH and frequency of monitoring based on the CKD category are shown in Table 63-6.[17] The most appropriate strategy is to evaluate trends in all these key CKD-MBD parameters to determine a reasonable treatment approach. The guideline emphasizes to avoid hypercalcemia based on evidence linking higher calcium levels with mortality and nonfatal CV events. The recommendation for phosphorus is to maintain levels “toward normal” based on evidence linking both high and low phosphate concentrations with increased mortality. Despite this association with higher mortality, the effect of phosphorus lowering with therapy (ie, phosphate binders) has not consistently demonstrated improved hard outcomes such as reduced mortality.[51,52]

TABLE 63-6

KDIGO Monitoring and Goals for Calcium, Phosphorus, and Parathyroid Hormone

		Chronic Kidney Disease Stage		
Parameter	**G3**	**G4**	**G5**	**ESKD**
Corrected calcium[a] Monitoring frequency[b] Goal	Every 6-12 months Avoid hypercalcemia [2C]	Every 3-6 months Avoid hypercalcemia [2C]	Every 1-3 months Avoid hypercalcemia [2C]	Every 1-3 months Avoid hypercalcemia [2C]
Phosphorus Monitoring frequency[b] Goal	Every 6-12 months Toward the normal range [2C]	Every 3-6 months Toward the normal range [2C]	Every 1-3 months Toward the normal range [2C]	Every 1-3 months Toward the normal range [2C]
Intact PTH Monitoring frequency[b] Goal	Based on baseline level and CKD progression Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 6-12 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3-6 months Avoid progressively rising levels or levels persistently above the upper limit of normal [2C]	Every 3-6 months 2-9 times the upper normal limit [2C]

Evidence grading in brackets.

[a]Corrected for albumin.

[b]Not graded.

Data from Reference 17.

Clinicians involved in the care of patients with CKD should know which PTH assays are available in their facilities. PTH is secreted from the parathyroid gland as intact PTH, an 84-amino-acid peptide chain (1-84 PTH) that is biologically active, and as smaller carboxy-terminal PTH fragments.[53] Circulating levels of these fragments (eg, 7-84 PTH) may increase substantially in patients with CKD and actively antagonize the effects of 1 to 84 PTH. The available immunoradiometric assays measure not only the intact PTH molecule but also fragments, which may lead to overestimation of biologically active PTH. While correction factors have been proposed, they cannot be uniformly applied to all commercially available assays and thus inconsistent results are common. The variability in PTH measurements and lack of evidence to support a specific target are part of the rationale for the KDIGO recommendation to monitor trends in serum PTH to guide treatment decisions. The optimal PTH in patients with CKD stages G3a-G5 is unclear. An increase in PTH is expected in response to declining kidney function and the desired phosphaturic effects; therefore, the guideline specifies that PTH levels *persistently* above the upper limit of normal and *progressively rising* should warrant a treatment decision. KDIGO recommends that PTH values for ESKD patients be within two to nine times the upper limit of the normal range, which corresponds to a PTH of approximately 130 to 600 pg/mL (ng/L; 14-64 pmol/L).[17] PTH values above 600 pg/mL (ng/L; 64 pmol/L) have been associated with higher CV mortality and hospitalizations.[54]

Monitoring of alkaline phosphatase activity is also recommended as this test may serve as a gauge of a patient's response to therapy and/or bone

turnover status. Avoiding the development of vascular calcification and calciphylaxis is also important as treatment options for this complication once it develops are extremely limited and the associated mortality is high.

Nonpharmacologic Therapy

Dietary Phosphorus Restriction

Dietary phosphorus restriction is a first-line intervention for management of hyperphosphatemia and should be initiated for most patients with CKD G3-G5.[17] The challenge with dietary restriction of phosphorus is providing enough protein to prevent malnutrition, a common problem in the ESKD population because dialysis patients require a higher protein intake (1.2-1.3 g/kg/day) and foods high in phosphorus are generally high in protein. An additional consideration is the source of phosphorus, organic versus inorganic. Inorganic sources such as from frozen meals and processed foods include preservatives or additives used during food processing, whereas organic sources such as from meat and plant sources typically do not and may be a better option. Dietary supplements and certain brands of medications also contain phosphate (eg, amlodipine, codeine) and may contribute to phosphate intake.[55] One of the most common obstacles to dietary phosphorus restriction is patient nonadherence because of the poor palatability of the allowed foods. Regular counseling by a dietitian is ideal to design a realistic diet that works with the patient's lifestyle and considers nutritional goals.

Dialysis

HD and PD lower serum phosphorus and calcium, the extent of which is dependent on the concentration of each in the dialysate and the duration of dialysis. It is suggested that the dialysate calcium concentration be between 2.5 and 3 mEq/L (1.25 and 1.5 mmol/L).[17] Removal of phosphorus does occur with dialysis (~2.5-3.5 g/wk, dependent on the dialysis prescription); however, conventional dialysis alone does not usually control hyperphosphatemia.[56] Patients on daily HD or nocturnal HD who typically have longer and/or more frequent dialysis sessions have better phosphorus control and require fewer phosphate-binding agents and in some cases may even require phosphate supplementation.

Parathyroidectomy

Parathyroidectomy is a therapeutic option for those patients with persistently elevated PTH associated with hypercalcemia and/or hyperphosphatemia who are refractory to medical therapy (a grade 2B recommendation).[17] Surgical approaches include either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of parathyroid tissue to an accessible site, such as the forearm. Postoperative hypocalcemia, hypophosphatemia, and hypomagnesemia may occur because of a marked increase in bone production in relation to bone absorption ("hungry bone syndrome"). Following surgery, frequent monitoring of calcium and phosphorus is necessary. Treatment with supplemental calcium and vitamin D may be required for weeks or months.

While a parathyroidectomy is indicated for refractory patients, these patients may experience significant morbidity following the procedure. In a study of over 4,400 ESKD patients who underwent a parathyroidectomy, there was an increase in hospitalizations (particularly for acute myocardial infarction and dysrhythmia) and emergency room visits for treatment of hypocalcemia in the year following the procedure.[57] For some patients, a parathyroidectomy may be ineffective and there is also the risk of over suppression of PTH and prolonged hypocalcemia.[58]

Pharmacologic Therapy

Patients with CKD-MBD usually require a combination of dietary intervention, phosphate-binding medications, vitamin D, and calcimimetic therapy (for ESKD patients).

Phosphate-Binding Agents

Phosphate-binding agents are used in addition to dietary phosphorus restriction to limit GI absorption. These agents are indicated for CKD patients with progressive or persistent hyperphosphatemia. For many patients, the pill burden with phosphate-binding agents contributes to nonadherence and efforts should be made to simplify the regimen when possible. The cost of phosphate binders is also significant, contributing to over 1.5 billion in Medicare costs for US dialysis patients and CKD patients with Medicare Part D.[52]

Pharmacology and Mechanism of Action

Drugs that bind dietary phosphorous in the GI tract form insoluble phosphate compounds that are excreted in feces, thus reducing dietary phosphorus absorption. Patients must be instructed to take these agents with meals to maximize the binding of phosphorus from dietary sources. A variety of phosphate-binding agents with varying binding affinity are available including elemental calcium, iron, and lanthanum-containing compounds, and the nonelemental agent sevelamer (Table 63-7). Estimates of phosphate-binding equivalent doses relative to 1 g of calcium carbonate have been reported based on the commonly available tablet or capsule strengths of each binder (calcium acetate 667 mg = 0.67; lanthanum 500 mg = 1.0, sevelamer carbonate 800 mg = 0.60, sucroferric oxyhydroxide 500 mg = 1.6, ferric citrate 210 mg = 0.64, aluminum hydroxide 500 mg = 0.75, and aluminum carbonate 500 mg = 0.95).[52,59]

TABLE 63-7

Phosphate-Binding Agents for Treatment of Hyperphosphatemia in Chronic Kidney Disease Patients

Category	Drug	Brand Name	Compound Content	Starting Doses	Dose Titration[a]	Comments[b]
Calcium-based binders	Calcium acetate (25% elemental calcium)	PhosLo	25% Elemental calcium (169 mg elemental calcium per 667 mg capsule)	1,334 mg three times a day with meals	Increase or decrease by 667 mg meal (169 mg elemental calcium)	Comparable efficacy to calcium carbonate with lower dose of elemental calcium Approximately 45 mg phosphorus bound per 1 g calcium acetate Evaluate for drug interactions with calcium
		Phoslyra	667 mg calcium acetate per 5 mL			
	Calcium carbonate[c]	Tums, Os-Cal, Caltrate	40% Elemental calcium	0.5-1 g (elemental calcium) three times a day with meals	Increase or decrease by 500 mg/meal (200 mg elemental calcium)	Dissolution characteristics and phosphate binding may vary from product to product Approximately 39 mg phosphorus bound per 1 g calcium carbonate Evaluate for drug interactions with calcium
Iron-based binders	Ferric citrate	Auryxia	210 mg elemental iron per tablet (= 1	420 mg ferric iron three times daily	Increase or decrease dose by 1	May increase serum iron, ferritin, and TSat May cause discolored

			g ferric citrate)	with meals	or 2 tablets per meal	(dark) stools Evaluate for drug interactions with iron
	Sucroferric oxyhydroxide	Velphoro	500 mg elemental iron per chewable tablet (= 2.5g succroferric oxyhydroxide)	500 mg three times daily with meals	Increase or decrease by 500 mg/day	May cause discolored (dark) stools Evaluate for drug interactions with iron
Resin binders	Sevelamer carbonate	Renvela	800 mg tablet 0.8 and 2.4 g powder for oral suspension	800-1,600 mg three times a day with meals (once-daily dosing also effective)	Increase or decrease by 800 mg/meal	Also lowers low-density lipoprotein cholesterol Consider in patients at risk for extraskeletal calcification Risk of metabolic acidosis with sevelamer hydrochloride (less risk with carbonate formulation) May interact with cipro and mycophenolate mofetil
	Sevelamer hydrochloride	Renagel	400 and 800 mg caplets	800-1,600 mg three times a day with meals	Increase or decrease by 800 mg/meal	
Other elemental binders	Lanthanum carbonate	Fosrenol	500, 750, and 1,000 mg chewable tablets 750 and 1,000 mg oral powder	1,500 mg daily in divided doses with meals	Increase or decrease by 750 mg/day	Potential for accumulation of lanthanum due to GI absorption (long-term consequences unknown) Evaluate for drug interactions (eg, cationic antacids, quinolone antibiotics)
	Aluminum hydroxide (NOT PREFERRED)	AlternaGel	Content varies (range 100-600 mg/unit)	300-600 mg three times a day with meals	Not for long-term use requiring titration	Not a first-line agent; risk of aluminum toxicity; do not use concurrently with citrate-containing products

						Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders Evaluate for drug interactions

TSat, transferrin saturation.

[a]Based on phosphorus levels, titrate every 2 to 3 weeks until phosphorus goal is reached.

[b]GI side effects are possible with all agents (eg, nausea, vomiting, abdominal pain, diarrhea, or constipation).

[c]Multiple preparations available that are not listed.

Efficacy

Oral calcium compounds are commonly used agents for control of serum phosphorus. Calcium carbonate and calcium acetate are the primary preparations used. Calcium citrate is also available but not used as a binder since the citrate component increases aluminum absorption and may cause more GI side effects. Calcium carbonate is marketed in a variety of dosage forms and is relatively inexpensive. Unfortunately, many calcium carbonate products are considered food supplements and thus do not meet US Pharmacopeia (USP) disintegration and dissolution requirements. In general, nationally advertised brands do meet these requirements, but it is difficult to determine whether private labels or house brands conform to these standards. Variability in gastric pH may also affect disintegration or dissolution, and thus phosphate-binding efficacy. Calcium carbonate is more soluble in an acidic medium and should be administered prior to meals when stomach acidity is highest. In addition, acid-suppressing agents such as ranitidine and proton pump inhibitors may reduce the phosphate-binding activity of calcium carbonate by increasing gastric pH. For patients with hypocalcemia, calcium carbonate or calcium acetate may also be given as a calcium supplement taken between meals to promote calcium absorption. This is a common scenario for patients following a parathyroidectomy.

Sevelamer is a nonabsorbable, nonelemental hydrogel phosphate-binding agent approved for ESKD patients, which effectively lowers phosphorus and has also been shown to lower LDL and increase HDL cholesterol. Sevelamer hydrochloride carries the risk of metabolic acidosis, a problem that has been overcome with development of the carbonate formulation. Sevelamer carbonate also comes in a powder formulation, which is a good option for many patients unable to swallow tablets.

Most of the comparative studies to date have focused on calcium-based binders versus sevelamer, which was the first non-calcium binder made available in the United States. The chronic use of calcium-containing phosphate binders promotes progression of vascular calcification; however, not all studies support this finding and this effect may occur with non-calcium–containing binders as well.[52] Available studies have more consistently shown a significant increase in coronary artery calcification with calcium-containing binders compared to sevelamer.[60] The effect of binder choice on mortality, particularly on CV mortality, is also controversial as studies evaluating this outcome are limited. Results of a meta-analysis showed that all cause death and risk of hypercalcemia were lower in dialysis patients receiving sevelamer when compared with calcium-based binders.[51] Fatal and nonfatal cardiovascular events, however, did not differ for ESKD patients receiving sevelamer compared to calcium acetate in an observational cohort study.[61] KDIGO suggests restricting the dose of calcium-based binders (a grade 2B recommendation); however, a maximum dose was not defined and this is left to clinical judgement.[17]

Lanthanum carbonate is a phosphate binder approved for patients with ESKD and has demonstrated efficacy in controlling phosphorus and maintaining PTH in the target range with less risk of hypercalcemia than calcium-containing binders.[17] The initial daily dose of 1,500 mg (administered in divided doses with meals) is often titrated to a range of 1,500 to 3,000 mg to maintain target phosphorus. The poor GI absorption, which limits

systemic effects, and high binding capacity with phosphorus make this an attractive phosphate-binding agent, particularly when calcium-containing binders are not recommended due to hypercalcemia. Lanthanum is available as a chewable tablet, which may be appealing for some patients.

Ferric citrate and sucroferric oxyhydroxide are the newest iron-based phosphate-binding agents approved for ESKD patients. Sucroferric oxyhydroxide effectively lowers phosphorus over a long-term (1-year) period and may have a lower pill burden compared to other agents.[62] It is also available as a chewable tablet. Ferric citrate effectively lowers phosphorus and also offers the advantage of increasing iron indices (TSat and ferritin) while lowering IV iron and ESA use when compared to other binders and ferrous sulfate.[63-65] This agent is approved for treatment of both hyperphosphatemia in ESKD patients and for iron deficiency anemia in patients with CKD not on dialysis. Another potential advantage of ferric citrate (and of iron supplementation in general) being explored is reduction in FGF23 that has been observed.[64] This finding is of interest given the associated between FGF23 and adverse outcomes.

Aluminum salts were widely used in the 1980s as phosphate-binding agents because of their high binding potency. Due to the potential for accumulation and toxicities in patients with CKD, they should not be used as first-line agents. KDIGO recommends avoiding the long-term use of aluminum-containing binders in all patients with CKD stage G3a-G5D (a 1C recommendation).[17]

Magnesium-containing antacids are also effective phosphate binders and may decrease the amount of calcium-containing binders necessary for control of phosphorus; however, they are not preferred due to the frequent occurrence of GI side effects (ie, diarrhea) and the potential for magnesium accumulation.

Other agents that have been evaluated for their phosphate binding effects and potential use for prevention and treatment of hyperphosphatemia in CKD patients include nicotinamide and tenapanor. Nicotinamide is a metabolite of nicotinic acid that inhibits the gastrointestinal sodium-dependent phosphate transporter, NaPi2b. This agent has been studied in hemodialysis patients with some promising results in terms of phosphorus-lowering effects; however, lack of robust clinical data to support consistent phosphate lowering and adverse effects may limit effectiveness and tolerability.[66-68] Tenapanor is an inhibitor of intestinal sodium/hydrogen exchanger 3 (NHE3) that blocks paracellular transport of phosphate across the intestinal lumen. This agent is approved for treatment of irritable bowel syndrome with constipation, but has also been studied in hemodialysis patients as a single agent and as an add-on therapy to current phosphate binder treatments.[69-71] Phosphate-lowering effects have been consistently demonstrated with diarrhea as the most frequent adverse effect. In 2021, the FDA did not grant approval of this agent for control of phosphorus in dialysis patients due to what was considered a small treatment effect with unclear clinical significance.

Adverse Effects

Adverse effects of all available phosphate binders are generally limited to constipation, diarrhea, nausea, vomiting, and abdominal pain. The risk of hypercalcemia may necessitate restriction of calcium-containing binder use and/or a reduction in dietary intake. Aluminum binders have been associated with CNS toxicity and the worsening of anemia, whereas magnesium binder use may lead to hypermagnesemia and hyperkalemia; therefore, aluminum and magnesium are not recommended for regular use in patients with kidney disease. The potential for iron overload should also be considered with ferric citrate given the effects on increasing iron indices. Accumulation of lanthanum tablets in the GI tract of a patient who swallowed these tablets resulted in severe complications; therefore, counsel patients to chew these tablets.[72] The same counseling point applies for sucroferric oxyhydroxide.

Drug-Drug and Drug-Food Interactions

Calcium-containing phosphate-binding agents interfere with the absorption of several oral medications that are commonly prescribed for CKD patients, including iron, zinc, and quinolone antibiotics. Coadministration of sevelamer with ciprofloxacin and mycophenolate did result in a reduction in bioavailability of these agents and they should be taken at least 2 hours before sevelamer. Coadministration of lanthanum with tetracyclines, fluoroquinolones, levothyroxine, or drugs known to bind with cationic antacids may result in decreased bioavailability of these agents. The iron-containing products ferric citrate and sucroferric oxyhydroxide also have the potential for drug interactions due to the iron component. In general, it is rational to separate the administration time of oral medications for which a reduction in bioavailability has a clinically significant effect (eg, quinolones) from phosphate binders by at least 1 hour before or 3 hours after administration of the phosphate binder. Many phosphate binders are marketed as antacids or calcium supplements, and often CKD patients do not know why they have been prescribed these agents. Regular patient counseling is essential to improve adherence and minimize the potential for drug interactions.

Dosing and Administration

Initial dosing regimens for phosphate-binding agents and suggested dose titration schemes are shown in Table 63-7. Doses should be titrated to achieve the recommended serum phosphorus concentrations in conjunction with dietary intervention and dialysis (for ESKD patients).

Vitamin D Therapy

Vitamin D compounds available in the United States include nutritional vitamin D (ergocalciferol [D_2] and cholecalciferol [D_3]), the prohormone calcifediol [25(OH)D_3], active vitamin D (calcitriol [D_3]), and vitamin D analogs (paricalcitol and doxercalciferol [both D_2]) (Table 63-8). Nutritional vitamin D (NVD) is derived from dietary plant (D_2) and animal (D_3) sources, or from supplements. While this chapter focuses on the role of NVD and FDA-approved vitamin D formulations for the management of mineral homeostasis, there are several other therapeutic uses for vitamin D (eg, for CV and immune-related effects) and other analogs available outside the United States which are not discussed (eg, alfacalcidol).

TABLE 63-8

Vitamin D Agents

Generic Name	Brand Name	Form of Vitamin D	Dosage Forms	Initial Dose	Dosage Range	Frequency of Dosing or Dose Titration[a]
Nutritional Vitamin D						
Ergocalciferol	Drisdol	D_2	po	Varies based on 25(OH)D levels	400-50,000 international units	Daily (doses of 400-2,000 international units)
Cholecalciferol[b]	Generic	D_3	po			Weekly or monthly for higher doses (50,000 international units)
Calcifidiol	Rayaldee	D_3	po	30 ug daily	30-60 ug	Increase after 3 months if PTH above desired range
Calcifediol Rayaldee D_3 po 30 µg daily 30-60 µg Increase after 3 months if PTH above desired range						
Vitamin D and Analogs						
Generic Name	**Brand Name**	**Form of Vitamin D**	**Dosage Forms**	**Initial Dose[c,d]**	**Dosage Range**	**Dose Titration[a]**
Calcitriol	Rocaltrol	D_3	po	0.25 µg daily	0.25-5 µg	Increase by 0.25 µg/day at 4- to 8-week intervals
	Calcijex		IV	1-2 µg three times per week	0.5-5 µg	Increase by 0.5-1 µg at 2 to 4-week intervals

Doxercalciferol[e]	Hectorol	D_2	po	ND-CKD: 1 µg daily ESKD: 10 µg three times per week	5-20 µg	Increase by 0.5 µg at 2-week intervals for daily dosing or by 2.5 µg at 8-week intervals for three times per week dosing
			IV	ESKD: 4 µg three times per week	2-8 µg	Increase by 1-2 µg at 8-week intervals
Paricalcitol	Zemplar	D_2	po	ND-CKD: 1 µg daily or 2 µg three times per week if PTH ≤500 pg/mL (ng/L; 54 pmol/L); 2 µg daily or 4 µg three times per week if PTH >500 pg/mL (ng/L; 54 pmol/L)	1-4 µg	Increase by 1 µg (for daily dosing) or 2 µg (for three times per week dosing) at 2- to 4-week intervals
			IV	ESKD: 0.04-1 µg three times per week	2.5-15 µg	Increase by 2-4 µg at 2- to 4-week intervals

ESKD, end-stage kidney disease; ND-CKD, non-dialysis chronic kidney disease; PTH, parathyroid hormone.

[a]Based on PTH, calcium and phosphorus levels. Decreases in dose are necessary if PTH is oversuppressed and/or if calcium and phosphorus are elevated.

[b]Multiple preparations are available that are not listed.

[c]Dose ratios are as follows: 1:1 for IV paricalcitol to oral doxercalciferol, 1.5:1 for IV paricalcitol to IV doxercalciferol, and 1:1 for IV to oral calcitriol.

[d]Daily orally dosing most common for ND- CKD patients, IV dosing three times per week more often used in the hemodialysis population.

[e]Prodrug that requires activation by the liver.

Pharmacology and Mechanism of Action

Vitamin D is a cholesterol derivative and is transported in the circulation by vitamin D–binding protein. The process of vitamin D metabolism is shown in Fig. 63-3. Both endogenously synthesized D_3 and NVD compounds (as D_2 or D_3) are converted in the liver to 25(OH)D, by the 25-hydroxylase enzyme. The 25(OH)D form is subsequently converted to the biologically active form 1,25-dihydroxyvitamin D (either D_2 or D_3 depending on the parent compound) by the 1-α-hydroxylase enzyme. This conversion occurs primarily in the kidney, but this enzyme is also present in extrarenal tissues. It is not clear whether active vitamin D produced in extrarenal tissue exerts its effects only locally or contributes to the systemic endocrine functions. It is the concentration of 25(OH)D that is most commonly measured clinically to diagnose vitamin D deficiency. The 25(OH)D form is available as calcifediol, an extended release oral formulation of the prohormone, indicated for patients with CKD G3 or G4 with low 25(OH)D levels (<30 ng/mL [75 nmol/L]).

Calcitriol and the vitamin D analogs bind to the vitamin D receptors (VDRs), which are located in many organ systems including the parathyroid glands, intestine, bone, kidney, heart, nervous, and immune systems. When vitamin D binds to the VDR, there is a conformational change in the VDR that allows for interaction of the receptor with the retinoid X receptor (RXR), a transcriptional factor.[73] The VDR-RXR complex binds to DNA sequences in target genes to either promote or inhibit transcription depending on the organ system. Vitamin D inhibits or suppresses PTH synthesis and also stimulates absorption of serum calcium by intestinal cells. As a result, the serum calcium concentration is raised, which decreases PTH secretion by the parathyroid glands. The set point for calcium (ie, the calcium concentration at which PTH secretion is decreased by 50%), which is generally raised in those with CKD-MBD, is lowered when active vitamin D therapy is initiated. This results in a lower ionized calcium concentration becoming effective at suppressing secretion of PTH. Unfortunately, the enhanced GI absorption of calcium and phosphorus associated with calcitriol therapy may lead to hypercalcemia and hyperphosphatemia, which are associated with soft-tissue and vascular calcifications.

The unique interactions of vitamin D with the VDRs have led to the development of vitamin D analogs that vary in their affinity for the VDRs. Paricalcitol

and doxercalciferol retain activity with vitamin D receptors on the parathyroid gland to effectively lower PTH, but have less risk of hypercalcemia and hyperphosphatemia due to their lower intestinal activity. Paricalcitol differs from calcitriol by the absence of the exocyclic carbon 19 and the fact that it is a vitamin D_2 derivative (19-nor-1,25-dihydroxyvitamin D_2). This compound is active as given. Doxercalciferol, however, is a prohormone that does require activation by CYP27 in the liver to form the major active D_2 metabolite 1,25-dihydroxyvitamin D_2 (see Fig. 63-3).

Pharmacokinetics

Oral absorption of calcitriol occurs rapidly; therefore, both oral and IV therapies are reasonable options for treatment of CKD-MBD. The half-life of active calcitriol ranges from 15 to 38 hours in patients with ESKD.[74] The half-lives of paricalcitol and doxercalciferol are approximately 15 hours and 32 to 37 hours, respectively.[75,76] These agents are extensively bound to plasma proteins and not removed by dialysis.

Efficacy

Calcitriol, paricalcitol, and doxercalciferol are all effective in lowering PTH in patients with CKD; however, the trade-off is the undesired effect of raising calcium and phosphorus concentrations due to increased intestinal absorption. Although these effects are less likely with paricalcitol and doxercalciferol, elevated calcium concentrations have been observed. An all-cause and CV survival benefit has also been reported with these agents in both CKD and ESKD patients in observational studies.[77] These survival benefits, however, have not been substantiated in randomized clinical trials based on meta-analysis of available data.[78] KDIGO does not advocate for routine use of calcitriol and vitamin D analogs in the ND- CKD population (a 2C recommendation) and suggests that they be reserved for patients with CKD stages G4-G5 (a recommendation that was not graded). These agents may be used in conjunction with calcimimetics when warranted in the dialysis population (a 2B recommendation).

A review and meta-analysis in CKD patients (including ESKD patients) reported that NVD supplementation was associated with an improvement in 25(OH)D levels and decreased PTH without significant hypercalcemia or hyperphosphatemia in ND- CKD patients[79]; however, this has not been a consistent finding. In ESKD patients, NVD has resulted in increased levels of 25(OH)D and a decrease in PTH, which suggests a potential role of extrarenal pathways of vitamin D activation; however, these patients typically also require active vitamin D or analog therapy. Calcifediol has been shown to lower PTH with relatively minimal effects on serum calcium and phosphorus in stage G3-G4 CKD, which is the reason it has gained approval in ND- CKD patients to treat 25(OH)D deficiency.[80] The survival benefit of correcting vitamin D deficiency with NVD in the CKD population is unknown. The recommendation by KDIGO is that confirmed 25(OH)D deficiency in patients with CKD G3a-G5D be corrected using treatment strategies in the general population (a 2C recommendation), which includes NVD therapies.[17,81]

Adverse Effects

Although all agents are effective in suppressing PTH, they may cause hypercalcemia and hyperphosphatemia, an effect that is most likely with calcitriol. Oversuppression of PTH and inducement of adynamic bone disease are also distinct possibilities.

Drug-Drug and Drug-Food Interactions

Cholestyramine may reduce the absorption of orally administered calcitriol and doxercalciferol. In vitro data suggest that paricalcitol is metabolized by the hepatic enzyme CYP3A4 and thus it has the potential to interact with other agents that are metabolized by this enzyme. Caution is also advised when CYP3A4 inhibitors are given to those receiving doxercalciferol since hydroxylation of this precursor agent may be inhibited.

Dosing and Administration

Despite limited evidence, KDIGO guidelines support administering NVD to patients with CKD G3a-G5 and ESKD with vitamin D deficiency or insufficiency (a grade 2C recommendation).[17] Calcitriol, doxercalciferol, or paricalcitol should be administered when PTH remains elevated despite the achievement of adequate 25(OH)D levels. ESKD patients require calcitriol, doxercalciferol, or paricalcitol.

Calcitriol by either the oral or the IV route may be administered daily (usually 0.25-1 µg/day) or using a pulse dosing (0.5-2 µg 2 to 3 times/wk) approach. Recommended doses of available NVD and analogs and suggested dose titration schemes are shown in Table 63-8. Prior to starting therapy, the serum calcium and phosphorus should be within the normal range. This does not mean that vitamin D therapy should be withheld or discontinued

in all patients with elevated calcium and phosphorus values, but rather that use of agents with a lower risk of hypercalcemia and hyperphosphatemia and more prudent use of phosphate binders to lower calcium and phosphorus may be necessary in such patients. Dose adjustments of vitamin D should be made every 2 to 4 weeks based on PTH concentrations and trends in calcium and phosphorus.

Calcimimetics

Cinacalcet hydrochloride (Sensipar) and etelcalcetide (Parsabiv) are calcimimetic agents approved for treatment of secondary hyperparathyroidism in CKD patients on dialysis. Cinacalcet is available as an oral agent, whereas etelcalcetide is an IV formulation. Both agents are approved for use only in dialysis patients.

Pharmacology and Mechanism of Action

Cinacalcet and etelcalcetide work through their interactions on the calcium-sensing receptor (CSR) located on the surface of the chief cells of the parathyroid gland. Cinacalcet works as an allosteric modulator of the CSR though binding to the transmembrane domain of the receptor while etelcalcetide binds directly to the extracellular domain resulting in increased sensitivity of the receptor to extracellular calcium (ie, lowering the threshold for receptor activation by calcium) and subsequently reducing PTH secretion.[82]

Pharmacokinetics

Cinacalcet peak concentrations are observed 2 to 6 hours following oral administration. Its elimination half-life is approximately 30 to 40 hours and steady-state plasma concentrations are achieved in approximately 7 days. It has a large volume of distribution (~1,000 L) and is 93% to 97% bound to plasma proteins, thus removal by dialysis is negligible. Cinacalcet is metabolized by the liver, specifically by the cytochrome P450 isoenzymes CYP3A4, CYP2D6, and CYP1A2.[83] Etelcalcetide has a half-life of 3 to 4 days and plasma levels reach steady state in several weeks.[84] This agent is not metabolized by CYP isoenzymes, but is cleared by renal excretion. Unlike cinacalcet this agent is cleared by hemodialysis.

Efficacy

In clinical trials conducted predominantly in dialysis patients, cinacalcet significantly decreased PTH, calcium, and phosphorus, regardless of the severity of secondary hyperparathyroidism. In ND- CKD patients cinacalcet reduced PTH, but was associated with a high incidence of hypocalcemia and hyperphosphatemia; thus, this agent is not approved for use in non-dialysis CKD patients. Cinacalcet may be used as a single agent to control hyperparathyroidism in ESKD patients; however, combined therapy with vitamin D is often necessary to achieve target PTH, calcium, and phosphorus values. In the ADVANCE trial, cinacalcet plus low-dose active vitamin D increased coronary artery calcification scores but to a lesser degree than its comparator calcitriol alone.[85] A decrease in all-cause and CV mortality was also suggested by results of an observational study in HD patients prescribed cinacalcet in addition to vitamin D compared with those on vitamin D alone.[86] While these findings were promising, they were not supported by the EVOLVE trial (the Evaluation of Cinacalcet Therapy to Lower CV Events), a prospective study which revealed that cinacalcet did not significantly reduce the risk of all-cause mortality or major CV events in patients with CKD 5HD.[87] There has been much debate with regard to the design and analysis of the EVOVLE trial and the interpretation of the findings with subsequent sub-analyses of the data to evaluate other outcomes such as reduction in FGF23 and risk of hypocalcemia.[88-90]

Etelcalcetide is effective in lowering PTH in hemodialysis patients with more long-term data (up to 12 months) showing sustained efficacy and safety.[91-93] Like cinacalcet, this agent also lowers calcium and phosphorus but has also been shown to lower FGF23 to a greater extent.[91,94,95] There have not been clinical studies to evaluate the effect of etelcalcetide on mortality or cardiovascular events; however, a small study in HD patients did show improvement in left ventricular hypertrophy that was associated with FGF23-lowering effects.[96]

Adverse Effects

The most frequent adverse events associated with cinacalcet are nausea and vomiting, which may account for nonadherence. Nausea and vomiting were reported with etelcalcetide in both the placebo-controlled trials and in the comparison trial with cinacalcet at a rate that was not significantly different compared with cinacalcet.[91,97] Since these agents lower serum calcium they should not be started if the corrected serum calcium is less than

the lower limit of normal, approximately 8.4 mg/dL (2.10 mmol/L). Serum calcium should be measured within 1 week after initiation or following a dose adjustment. Once the maintenance dose is established, serum calcium should be measured monthly. Potential manifestations of hypocalcemia include paresthesia, myalgia, cramping, tetany, and convulsions. Hypocalcemia may also lead to Q-T interval prolongation and ventricular arrhythmias, which further emphasizes the importance of regular calcium monitoring.

Drug-Drug and Drug-Food Interactions

Because cinacalcet is partially metabolized by CYP3A4, there is potential for drug interactions with agents that inhibit this pathway. Coadministration of cinacalcet and ketoconazole, a strong inhibitor of CYP3A4, results in a twofold increase in the area under the curve and maximum concentration. Cinacalcet is also a potent inhibitor of CYP2D6. As a result, dose adjustments of concomitant medications that are predominantly metabolized by this enzyme and have a narrow therapeutic index, such as flecainide, thioridazine, vinblastine, and most tricyclic antidepressants (eg, amitriptyline, desipramine), may be necessary. Concurrent administration of cinacalcet with desipramine increased desipramine exposure by approximately 260% in CYP2D6-extensive metabolizers.[83] Food has been shown to increase absorption of cinacalcet by up to 82% compared with fasting; therefore, this medication should be taken with meals to achieve the maximal effect.

There are no drug interactions reported with etelcalcetide. Of note, this agent is not a substrate or inhibitor of CYP isoenzymes or transporter proteins (eg, *P*-glycoprotein, organic anionic/cationic transporters).

Dosing and Administration

The recommended starting dose of cinacalcet is 30 mg orally once daily. Calcium and phosphorus should be measured at 1 week and PTH should be measured within 1 to 4 weeks after starting cinacalcet or adjusting the dose. The dose should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily until the desired PTH values are achieved and to maintain goal serum calcium concentrations. Patients with hepatic disease may require lower doses, since the cinacalcet half-life is approximately doubled in those with severe liver disease.[83] Cinacalcet is available as film-coated tablets containing 30, 60, or 90 mg.

Etelcalcetide should be initiated at a dose of 5 mg administered intravenously three times per week at the end of the hemodialysis treatment. Calcium and phosphorus should be measured 1 week after initiation and then every 4 weeks for maintenance therapy. PTH levels should be measured 4 weeks after initiation and then per protocol based on the practices of the dialysis center. If PTH levels are above the recommended target range and the corrected serum calcium is within the normal range, the dose of etelcalcetide should be increased in 2.5 or 5 mg increments up to a maximum dose of 15 mg. The dose should be decreased or temporarily discontinued in patients with PTH levels below the target range or in patients with a corrected calcium at or above 7.5 mg/dL (1.88 mmol/L) but less the lower limit of normal (8.4 mg/dL), without symptoms of hypocalcemia. Other interventions to increase calcium may be initiated if necessary (eg, altering vitamin D therapy and calcium supplementation). Etelcalcetide may be resumed once the PTH is within the target range and hypocalcemia has resolved, but at a lower dose. If the corrected calcium is below 7.5 mg/dL (1.88 mmol/L), then etalcalcitide should be discontinued and reinitiated at a dose 5 mg lower than the last administered dose once hypocalcemia has resolved. Patients who were receiving 2.5 or 5 mg should reinitiate therapy at a dose of 2.5 mg.[84]

Since etelcalcetide is removed by hemodialysis it should be administered at the end of the hemodialysis treatment and injected into the venous line of the dialysis circuit during or after rinse back. If a dose is missed (eg, due to a missed hemodialysis treatment), then that missed dose should not be administered, but the patient should resume the regular treatment schedule at the next hemodialysis session. If doses are missed for more than 2 weeks, then etelcalcetide should be restarted at the 5 mg dose.[84] If switching a patient from cinacalcet to etelcalcetide, then cinacalcet should be discontinued for at least 7 days prior to starting etelcalcetide. If switching patients from etelcalcetide to cinacalcet, etalcalcetide should be discontinued for at least 4 weeks prior to starting cinacalcet due to the long half-life of etalcalcetide.

Cardiovascular Complications of Chronic Kidney Disease

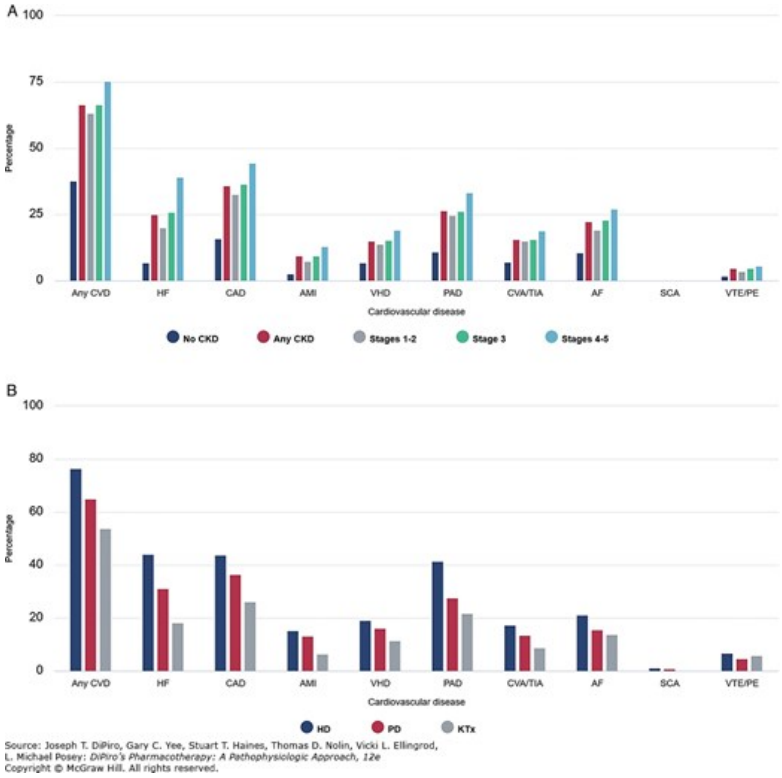
Cardiovascular Disease

Patients with CKD are at increased risk of CVD, independent of the etiology of their kidney disease. This greater burden of CVD in patients with CKD is illustrated in Fig. 63-5.[3] The prevalence of any form of CVD is greater as kidney disease progresses from CKD stages G1-G5 (Fig. 63-5a) and is highest in patients with ESKD (Fig. 63-5b). This burden of CVD is associated with much higher mortality rates. In general, CKD patients have a lower probability of

survival for all of the CVD conditions reported, with late stages of CKD being associated with the worst outcomes.[98] For example, the adjusted 2-year survival probability for patients with an AMI without a diagnosis of CKD is 71% versus 60% for CKD Stage 1 to 2 patients and 54% for CKD Stage 4 to 5 patients.[3] In addition to traditional risk factors for CVD such as diabetes mellitus/insulin resistance, dyslipidemia, hypertension, LVH, smoking, and obesity patients with CKD have other nontraditional risk factors including proteinuria, inflammation, anemia, and abnormal calcium and phosphate metabolism resulting in vascular calcification and oxidative stress.[98,99]

FIGURE 63-5

Prevalence of cardiovascular diseases in (A) Medicare patients ≥66 years by CKD status and stage, 2018 and (B) patients with ESKD by treatment modality.[3] (AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; CVD, cardiovascular disease; HD, hemodialysis; HF, heart failure; KTx, kidney transplant; PAD, peripheral arterial disease; PD, peritoneal dialysis; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism. *(Medicare 5% sample of patients aged 66 years and older, alive, without ESKD, and residing in the United States on 12/31/2018. Note: The data reported here have been supplied by the United States Renal Data System [USRDS].)*



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*

Unfortunately, the lack of randomized trials treating CVD in patients with CKD often leads to treatment decisions that are based on extrapolation from trials in non-CKD populations and from observational data in CKD patients and not robust evidence. Treatment approaches for CVD include strategies to mitigate the traditional and non-traditional risk factors for CVD. The lack of data specific to CKD is a reason for the absence of guidelines on management of CVD in patients with CKD. The 2013 KDIGO CKD guideline did include statement regarding select CVDs including ischemic heart disease and recommended that the level of care for ischemic heart disease offered to people with CKD should not differ from people without CKD (grade 1A recommendation) as the treatment of traditional risk factors in CKD patients is of benefit.[100] These patients should also receive the standard assessments and treatments such as statins for CKD 1-5 (non-dialysis), beta-blockers, ACEIs/ARBs, and antiplatelet agents (see Chapters 33 and 34). Clinicians should note that in the diagnosis of acute coronary syndrome, elevated serum troponins should be interpreted with caution in individuals with a GFR less than 60 mL/min/1.73 m^2 (<0.58 mL/s/m^2) because these markers are often elevated as a result of reduced kidney excretion (a grade 1B recommendation).

With regard to heart failure, KDIGO suggested that patients with CKD should receive standard heart failure therapies (Chapter 36); however, clinicians should be aware that RAAS blockade (eg, ACEI, ARB, neprilysin inhibitor/ARB, spironolactone, eplerenone) and diuretic therapy (eg, furosemide,

metolazone) may lead to significant changes in GFR and serum potassium concentrations. Such therapy should not be avoided, but closely monitored and put into the context of individual risks and benefits. With regard to the cardiac biomarkers of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) in individuals with a GFR less than 60 mL/min/1.73 m^2 (<0.58 mL/s/m^2) (CKD G3a-G5), it is recommended that serum concentrations be interpreted with caution with respect to diagnosis of heart failure and assessment of volume status (a grade 1B recommendation).

Aspirin (ASA) is recommended for secondary prevention in all patients with CKD based on decreased mortality in observational studies.[100,101] ASA is generally not recommended for primary prevention as compared to placebo or no treatment as it reduces the risk of myocardial infarction but not all-cause mortality, CV mortality, or stroke and increases the risk of major and minor bleeding.[102,103]

Also of importance with regard to cardiovascular disease in patients with CKD is the fact that non-dialysis CKD patients now have more therapies available to delay CKD progression including sodium-glucose co-transporter type 2 (SGLT2) inhibitors (eg, canagloflozin, dapagloflozin), glucagon-like-peptide-1 (GLP-1) receptor agonists, and mineralocorticoid receptor antagonists (eg, finerenone) (see Chapter 62 for further discussion). While the primary reason these agents are prescribed relates to slowing CKD progression, the positive cardiovascular outcomes associated with use of these agents are important when considering the potential benefits of selecting a given agent.

Hyperlipidemia

CKD with or without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism. Although the concentrations of LDL are not uniformly increased in patients with kidney disease, these patients produce small, dense LDL particles that are more susceptible to oxidation and more atherogenic than larger LDL subfractions. Other lipid abnormalities include low HDL, increased VLDL, and increased triglycerides.[104,105] In patients with nephrotic syndrome, the major lipid abnormalities are elevation of plasma total and LDL cholesterol, with or without low HDL cholesterol, and elevated triglycerides. See Chapter e66 for a detailed discussion of the management of proteinuria in patients with glomerular disease.

The KDIGO Lipid Guideline recommends that a complete fasting lipid profile be performed in all adults with newly identified CKD (a grade 1C recommendation).[106] Follow-up lipid levels are not recommended unless the information may alter management (eg, assessing adherence to therapy or assessing CV risk in a patient <50 years and not currently on a statin). Reduction in the risk of CV events in patients with CKD has only been demonstrated with statins or a statin plus ezetimibe combination.[107]

Statins in Chronic Kidney Disease

Statins have been shown to decrease mortality and CV events in ND- CKD patients; however, data are not as compelling in the ESKD population. Two trials (4D and AURORA) conducted in ESKD patients on hemodialysis did not show a benefit of statin therapy for primary prevention of cardiovascular events including nonfatal myocardial infarction, nonfatal stroke, and death from cardiac causes.[105,106] The Study of Heart and Renal Protection (SHARP) trial was conducted after these trials and was a primary prevention trial that evaluated the effects of combined simvastatin (20 mg) and ezetimibe (10 mg) compared with placebo on time to first major vascular event (nonfatal MI or cardiac death, any stroke, or revascularization) in patients with no history of MI or coronary revascularization and included patients with CKD (6,247) and ESKD (3,023).[107] In all patients receiving combined therapy during the 4.9-year follow-up period, there was a significant 17% reduction in the relative risk (RR) of major vascular events and a 32% reduction in LDL in the patients who were assessed as compliant with therapy (two-thirds were compliant). While overall these results are positive, the reduction in major atherosclerotic events was not significant for the dialysis subgroup, although the study was not powered to evaluate ESKD patients as a separate group. A subgroup analysis comparing dialysis versus non-dialysis patients showed no differences in the RR of CV events even after adjustment for the reduction in LDL. A subsequent meta-analysis of statins in dialysis patients indicated that they had no significant beneficial effect on major CV events, all-cause mortality, CV death, or myocardial infarction, and a trend toward increased strokes despite clinically relevant reductions in LDL cholesterol.[108] In contrast, a meta-analysis of statins in ND-CKD showed significant reductions in major CV events, CV death, all-cause mortality; myocardial infarction but uncertain effects on stroke.[109] Now there are also more data to support statins in non-dialysis CKD patients than in ESKD patients for secondary prevention of atherosclerotic cardiovascular events.[105,110]

The KDIGO Lipid guidelines[106] make the following recommendations:

1. In adults aged 18 to 49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (Level 2A): known coronary disease (myocardial infarction or coronary revascularization); diabetes mellitus; prior ischemic stroke; estimated 10-year incidence of coronary death or nonfatal myocardial infarction greater than 10%.

2. In adults older than 50 years with eGFR less than 60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation, we recommend treatment with a statin or statin/ezetimibe combination (Level 1A).

3. In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated (Level 2A). However, in patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued (Level 2C).

The 2018 American Heart Association and the American College of Cardiology (AHA/ACC) guidelines on cholesterol recognize CKD as a risk factor for CV events and recommend that treatment with a moderate-intensity statin (or moderate-intensity statin therapy plus ezetimibe) can be considered in patients with non-dialysis CKD between the ages of 40 and 75 years and 10-year CV risk of 7.5% or higher.[111]

In addition to some of the controversies with statin therapy in CKD, the newer cholesterol lowering agents for the management of hyperlipidemia to reduce atherosclerotic CVD such as the PCSK9 inhibitors have not been evaluated across the spectrum of CKD except in secondary analyses and further data are needed to evaluate potential benefits beyond lipid lowering in CKD patients.[105,110]

Pruritus

Chronic pruritus (or uremic pruritus/itching) is among the many complications that patients with advanced CKD endure and has long been a problem without a directly linked etiology, which has made determination of treatment options a challenge. The diagnosis is made in patients with CKD when all other potential comorbid conditions associated with pruritus have been ruled out. CKD-associated pruritus is estimated to occur in approximately 40% of ESKD patients, but this is thought to be an underestimate.[112] There is much variability in time of onset relative to dialysis, frequency of symptoms, and body distribution with up to 50% of patients experiencing generalized pruritis that is often symmetrical. Some patients experience more localized pruritus with the face, back, and access arm, but common sites include the legs, back, and scalp. Over time other complications may occur such as impetigo, ulcerations, and increased risk of infections.[113,114] Regardless of location pruritus has a negative effect on patient quality of life with sleep disturbances and depression associated with this condition.[112-114]

The mechanisms of pruritus are not fully understood, which is part of the reason multiple interventions have been attempted. The release of compounds by keratinocytes, immune cells, or neurons in the skin that promote inching (pruritogens) including histamine, prostaglandins, cytokines, neuropeptides, and protases has been proposed.[114] Imbalances in the endogenous opioid system, particularly peripherally distributed kappa opioid receptors, have been explored as playing a key role.[113] Pruritus has also been associated with inadequate dialysis, elevated PTH, calcium, and phosphorus; however, these associations are inconsistent and their correction does not necessarily correlate with resolution of pruritus.[113] Pharmacologic interventions that have been implemented to address CKD-associated pruritus include gabapentinoids, capsaicin, sertraline, mirtazapine, antihistamines, among other strategies, with variable success.[113]

9 Until recently, there was no approved therapy for uremic pruritus in the United States. Difelikefalin, a peripheral kappa opioid receptor agonist, exerts antipruritic effects by means of activation of kappa opioid receptors on peripheral neurons and immune cells. Reductions in itch intensity and improvements in sleep and quality of life were demonstrated in phase 3 clinical trials which lead to the larger scale trial to evaluate efficacy and safety of difelikefalin in 378 adult HD patients with moderate to severe pruritus. Patients received either difelikefalin 0.5 µg/kg or placebo three times per week and improvements in itching intensity scores compared to baseline over a 12-week period were evaluated. Significantly more patients receiving difelikeflain (52%) had what was deemed a clinically significant (3 point) decrease in itching intensity score compared to 31% in the placebo group (primary outcome). There was also improvement in quality of life.[115] Adverse effects included diarrhea, dizziness, and vomiting. Based on these data difelikefalin was approved in 2021 for treatment of moderate to severe CKD associated pruritus in HD patients. This agent is approved at a dose of 0.5 µg/kg administered intravenously into the venous line of the dialysis circuit at the end of each HD treatment since this agent is extensively removed by HD.[116] Post approval data and patient-reported outcomes with use of this agent will be of interest as difelikefalin begins to be used in clinical practice in the ESKD population.

CONCLUSION

Although efforts to delay progression of CKD are paramount, measures to diagnose and manage the associated secondary complications and comorbid conditions early in the course of the disease are also essential. There are many secondary complications of advanced CKD that worsen as kidney disease progresses. This chapter focused on common complications of advanced CKD for which pharmacologic therapies are available including anemia, CKD-MBD, and uremic pruritus. CV complications are also prevalent in the population with CKD and although data are sparse compared to the general population, mitigation strategies should be considered as CVD is the leading cause of mortality in patients with ESKD.

Involving a multidisciplinary team to address not only CKD but to effectively design and implement individual patient care plans often required in the CKD population that include extensive nonpharmacologic and pharmacologic interventions is logical. Pharmacists are well positioned to actively participate in the chronic disease and medication management of CKD and ESKD patients and should be part of the current and developing kidney care models within the nephrology environment.

ABBREVIATIONS

CERA	continuous erythropoietin receptor activator
CHOIR	Correction of Hb and Outcomes in Renal Insufficiency
CKD	chronic kidney disease
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
CV	cardiovascular
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis stimulating agent
ESKD	end-stage kidney disease
FGF-23	fibroblast growth factor-23
GFR	glomerular filtration rate
GI	gastrointestinal
Hb	hemoglobin
Hct	hematocrit
HD	hemodialysis
HIF	hypoxia inducible factor
HIF-PHI	HIF-prolyl hydroxylase inhibitors
KDIGO	Kidney Disease: Improving Global Outcomes

LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MBD	mineral and bone disorder
ND-CKD	non-dialysis CKD patients
NHCT	Normal Hematocrit Cardiac Trial
NVD	nutritional vitamin D
25(OH)D	25-hydroxyvitamin D
PD	peritoneal dialysis
PRCA	pure red cell aplasia
PTH	parathyroid hormone
ROD	renal osteodystrophy
RXR	retinoid X receptor
SUBQ	subcutaneous
sHPT	secondary hyperparathyroidism
TIBC	total iron-binding capacity
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSat	transferrin saturation
USRDS	United States Renal Data System
VDRs	vitamin D receptors
VLDL	very low-density lipoprotein

REFERENCES

1. St Peter WL, Guo H, Kabadi S, Gilbertson DT, Peng Y, Pendergraft T, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. *BMC Nephrol.* 2018;19. https://doi.org/10.1186/s12882-018-0861-1.

2. Lopes MB, Tu C, Zee J, Guedes M, Pisoni RL, Robinson BM, et al. A real-world longitudinal study of anemia management in non-dialysis-dependent chronic kidney disease patients: A multinational analysis of CKDopps. *Sci Rep.* 2021;11. https://doi.org/10.1038/s41598-020-79254-6.

3. United States Renal Data System, 2020 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, 2020.

4. Del Vecchio L, Minutolo R. ESA, iron therapy and new drugs: Are there new perspectives in the treatment of anaemia? *J Clin Med.* 2021;10:839. https://doi.org/10.3390/jcm10040839. [PubMed: 33670704]

5. The DOPPS Practice Monitor. www.dopps.org. Accessed August 1, 2021. n.d.

6. Karaboyas A, Morgenstern H, Waechter S, Fleischer NL, Vanholder R, Jacobson SH, et al. Low hemoglobin at hemodialysis initiation: An international study of anemia management and mortality in the early dialysis period. *Clin Kidney J.* 2020;13:425–433. https://doi.org/10.1093/ckj/sfz065. [PubMed: 32699623]

7. Babitt JL, Eisenga MF, Haase VH, Kshirsagar AV, Levin A, Locatelli F, et al. Controversies in optimal anemia management: Conclusions from a kidney disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int.* 2021;99:1280–1295. https://doi.org/10.1016/j.kint.2021.03.020. [PubMed: 33839163]

8. Gutiérrez OM. Fibroblast growth factor 23 and disordered vitamin D metabolism in chronic kidney disease: Updating the "trade-off" hypothesis. *Clin J Am Soc Nephrol.* 2010;5:1710–1716. https://doi.org/10.2215/CJN.02640310. [PubMed: 20507957]

9. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* 2009:S1–130.

10. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: Core Curriculum 2018. *Am J Kidney Dis.* 2018;71:423–435. https://doi.org/10.1053/j.ajkd.2017.09.026. [PubMed: 29336855]

11. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kidney Dis.* 2017;69:815–826. https://doi.org/10.1053/j.ajkd.2016.12.011. [PubMed: 28242135]

12. Locatelli F, Del Vecchio L. Are prolyl-hydroxylase inhibitors potential alternative treatments for anaemia in patients with chronic kidney disease? *Nephrol Dial Transplant*. 2020;35. https://doi.org/10.1093/ndt/gfz031.

13. Locatelli F, Fishbane S, Block GA, MacDougall IC. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *Am J Nephrol.* 2017;45:187–199. https://doi.org/10.1159/000455166. [PubMed: 28118622]

14. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Inter Suppl.* 2012;2:279–335.

15. Sheetz M, Barrington P, Callies S, Berg PH, McColm J, Marbury T, et al. Targeting the hepcidin-ferroportin pathway in anemia of chronic kidney disease. *Br J Clin Pharmacol.* 2019. https://doi.org/10.1111/bcp.13877.

16. Moorthi RN, Moe SM. CKD-mineral and bone disorder: Core curriculum 2011. *Am J Kidney Dis.* 2011;58:1022–1036. https://doi.org/10.1053/j.ajkd.2011.08.009. [PubMed: 22018457]

17. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1–59. https://doi.org/10.1016/j.kisu.2017.04.001.

18. Isakova T, Ix JH, Sprague SM, Raphael KL, Fried L, Gassman JJ, et al. Rationale and approaches to phosphate and fibroblast growth factor 23 reduction in CKD. *J Am Soc Nephrol.* 2015;26:2328–2339. https://doi.org/10.1681/asn.2015020117. [PubMed: 25967123]

19. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med.* 2018;379:399–400. https://doi.org/10.1056/NEJMc1807324. [PubMed: 30044942]

20. Portales-Castillo I, Kroshinksy D, Malhotra CK, Culbert-Costley R, Cozzolino MG, Karparis S, et al. Calciphylaxis—as a drug induced adverse event. *Expert Opin Drug Saf.* 2018. https://doi.org/10.1080/14740338.2019.1559813.

21. Jones G. Interpreting vitamin D assay results: Proceed with caution. *Clin J Am Soc Nephrol.* 2015;10:331–334. https://doi.org/10.2215/CJN.05490614. [PubMed: 25107951]

22. Collister D, Komenda P, Hiebert B, Gunasekara R, Xu Y, Eng F, et al. The effect of erythropoietin-stimulating agents on health-related quality of life in anemia of chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med.* 2016;164:472–478. https://doi.org/10.7326/m15-1839. [PubMed: 26881842]

23. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339:584–590. [PubMed: 9718377]

24. Besarab A, Goodkin DA, Nissenson AR. The normal hematocrit study—follow-up. *N Engl J Med.* 2008;358:433–434. [PubMed: 18216370]

25. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin-alfa in chronic kidney disease. *N Engl J Med.* 2006;355:2085–2098. [PubMed: 17108343]

26. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med.* 2006;355:2071–2084. [PubMed: 17108342]

27. FDA Drug Safety Communication: modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. Last updated 8/4/2017. http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm.

28. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: A meta-analysis. *Lancet.* 2007;369:381–388. [PubMed: 17276778]

29. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med.* 2009;361:2019–2032. [PubMed: 19880844]

30. Cizman B, Smith HT, Camejo RR, Casillas L, Dhillon H, Mu F, et al. Clinical and economic outcomes of erythropoiesis-stimulating agent hyporesponsiveness in the post-bundling era. *Kidney Med.* 2020;2. https://doi.org/10.1016/j.xkme.2020.06.008.

31. Souza E, Cho KH, Harris ST, Flindt NR, Watt RK, Pai AB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A paradigm shift for treatment of anemia in chronic kidney disease? *Expert Opin Investig Drugs*. 2020;29. https://doi.org/10.1080/13543784.2020.1777276.

32. Ratcliffe LEK, Thomas W, Glen J, Padhi S, Pordes BAJ, Wonderling D, et al. Diagnosis and management of iron deficiency in CKD: A summary of the NICE guideline recommendations and their rationale. *Am J Kidney Dis.* 2016;67:548–558. https://doi.org/10.1053/j.ajkd.2015.11.012. [PubMed: 26763385]

33. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol.* 2017;28:1851–1858. https://doi.org/10.1681/ASN.2016101053. [PubMed: 28082519]

34. Fishbane SN, Singh AK, Cournoyer SH, Jindal KK, Fanti P, Guss CD, et al. Ferric pyrophosphate citrate (Triferic) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. *Nephrol Dial Transpl.* 2015;30:2019–2026. https://doi.org/10.1093/ndt/gfv277.

35. Gupta A, Lin V, Guss C, Pratt R, Ikizler TA, Besarab A. Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. *Kidney Int.* 2015;88:1187–1194. https://doi.org/10.1038/ki.2015.203. [PubMed: 26154926]

36. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA.* 2015;314:2062–2068. https://doi.org/10.1001/jama.2015.15572. [PubMed: 26575062]

37. FDA drug safety communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm. Last accessed August 17, 2021.

38. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med.* 2019;380:447–458. https://doi.org/10.1056/NEJMoa1810742. [PubMed: 30365356]

39. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: Systematic review and meta-analysis. *Mayo Clin Proc.* 2015;90:12–23. https://doi.org/10.1016/j.mayocp.2014.10.007. [PubMed: 25572192]

40. Hougen I, Collister D, Bourrier M, Ferguson T, Hochheim L, Komenda P, et al. Safety of intravenous iron in dialysis: A systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2018;13:457–467. https://doi.org/10.2215/cjn.05390517. [PubMed: 29463597]

41. Ganz T, Aronoff GR, Gaillard CAJM, Goodnough LT, Macdougall IC, Mayer G, et al. Iron administration, infection, and anemia management in CKD: Untangling the effects of intravenous iron therapy on immunity and infection risk. *Kidney Med.* 2020;2:341–353. https://doi.org/10.1016/j.xkme.2020.01.006. [PubMed: 32734254]

42. Macdougall IC, Bhandari S, White C, Anker SD, Farrington K, Kalra PA, et al. Intravenous iron dosing and infection risk in patients on hemodialysis: A prespecified secondary analysis of the PIVOTAL trial. *J Am Soc Nephrol.* 2020;31:1118–1127. https://doi.org/10.1681/ASN.2019090972. [PubMed: 32253271]

43. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: Two open-label, randomised controlled trials. *Lancet Haematol.* 2017;4:e524–e533. https://doi.org/10.1016/S2352-3026(17)30182-5. [PubMed: 29032957]

44. Epogen. Package Insert. Amgen. Thousand Oaks, CA. 2018.

45. Macdougall IC, Roger SD, de Francisco A, Goldsmith DJ, Schellekens H, Ebbers H, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: New insights. *Kidney Int.* 2012;81:727–732. https://doi.org/10.1038/ki.2011.500. [PubMed: 22336988]

46. Macdougall IC, Casadevall N, Locatelli F, Combe C, London GM, Di Paolo S, et al. Incidence of erythropoietin antibody-mediated pure red cell aplasia: The Prospective Immunogenicity Surveillance Registry (PRIMS). *Nephrol Dial Transpl.* 2015;30:451–460. https://doi.org/10.1093/ndt/gfu297.

47. Mircera. Package Insert. Hoffmann-La Roche, Inc, South San Francisco, CA. 2018.

48. Hazzan AD, Shah HH, Hong S, Sakhiya V, Wanchoo R, Fishbane S. Treatment with erythropoiesis-stimulating agents in chronic kidney disease patients with cancer. *Kidney Int.* 2014;86:34–39. https://doi.org/10.1038/ki.2013.528. [PubMed: 24402094]

49. Aranesp. Package Insert. Amgen, Thousand Oaks, CA, 2018.

50. Wish JB. Hypoxia-inducible factor–prolyl hydroxylase inhibitors for the treatment of anemia in CKD: Additional pieces of the jigsaw puzzle. *Kidney Int Rep.* 2021;6:1751–1754. https://doi.org/10.1016/j.ekir.2021.05.017. [PubMed: 34308931]

51. Ruospo M, Palmer SC, Natale P, Craig JC, Vecchio M, Elder GJ, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev.* 2018;8:Cd006023. https://doi.org/10.1002/14651858.CD006023.pub3.

52. St Peter WL, Wazny LD, Weinhandl ED. Phosphate-binder use in US dialysis patients: Prevalence, costs, evidence, and policies. *Am J Kidney Dis.* 2018;71:246–253. https://doi.org/10.1053/j.ajkd.2017.09.007. [PubMed: 29195858]

53. Soliman M, Hassan W, Yaseen M, Rao M, Sawaya BP, El-Husseini A. PTH assays in dialysis patients: Practical considerations. *Semin Dial.* 2019;32:9–14. https://doi.org/10.1111/sdi.12743. [PubMed: 30168196]

54. Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: The DOPPS study. *Clin J Am Soc Nephrol.* 2015;10:98–109. https://doi.org/10.2215/cjn.12941213. [PubMed: 25516917]

55. Nelson SM, Sarabia SR, Christilaw E, Ward EC, Lynch SK, Adams MA, et al. Phosphate-containing prescription medications contribute to the daily phosphate intake in a third of hemodialysis patients. *J Ren Nutr.* 2017;27:91–96. https://doi.org/10.1053/j.jrn.2016.09.007. [PubMed: 27814946]

56. Daugirdas JT. Removal of phosphorus by hemodialysis. *Semin Dial.* 2015;28:620–623. https://doi.org/10.1111/sdi.12439. [PubMed: 26358370]

57. Ishani A, Liu J, Wetmore JB, Lowe KA, Do T, Bradbury BD, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol.* 2015;10:90–97. https://doi.org/10.2215/cjn.03520414. [PubMed: 25516915]

58. Wetmore JB, Liu J, Do TP, Lowe KA, Ishani A, Bradbury BD, et al. Changes in secondary hyperparathyroidism-related biochemical parameters and medication use following parathyroidectomy. *Nephrol Dial Transpl.* 2016;31:103–111. https://doi.org/10.1093/ndt/gfv291.

59. Daugirdas JT, Finn WF, Emmett M, Chertow GM. The phosphate binder equivalent dose. *Semin Dial.* 2011;24:41–49. https://doi.org/10.1111/j.1525-139X.2011.00849.x. [PubMed: 21338393]

60. St. Peter WL, Wazny LD, Weinhandl E, Cardone KE, Hudson JQ. A review of phosphate binders in chronic kidney disease: Incremental progress or just higher costs? *Drugs*. 2017;77:1155–1186. https://doi.org/10.1007/s40265-017-0758-5. [PubMed: 28584909]

61. Spoendlin J, Paik JM, Tsacogianis T, Kim SC, Schneeweiss S, Desai RJ. Cardiovascular outcomes of calcium-free vs calcium-based phosphate binders in patients 65 years or older with end-stage renal disease requiring hemodialysis. *JAMA Intern Med.* 2019;179:741–749. https://doi.org/10.1001/jamainternmed.2019.0045. [PubMed: 31058913]

62. St. Peter WL, Wazny LD, Weinhandl E, Cardone KE, Hudson JQ. A review of phosphate binders in chronic kidney disease: Incremental progress or just higher costs? *Drugs*. 2017;77:1155–1186. https://doi.org/10.1007/s40265-017-0758-5. [PubMed: 28584909]

63. Choi YJ, Noh Y, Shin S. Ferric citrate in the management of hyperphosphataemia and iron deficiency anaemia: A meta-analysis in patients with chronic kidney disease. *Br J Clin Pharmacol.* 2021;87:414–426. https://doi.org/10.1111/bcp.14396. [PubMed: 32470149]

64. Yokoyama K, Fukagawa M, Akiba T, Nakayama M, Ito K, Hanaki K, et al. Randomised clinical trial of ferric citrate hydrate on anaemia management in haemodialysis patients with hyperphosphataemia: ASTRIO study. *Sci Rep.* 2019;9:8877. https://doi.org/10.1038/s41598-019-45335-4. [PubMed: 31222044]

65. Womack R, Berru F, Panwar B, Gutiérrez OM. Effect of ferric citrate versus ferrous sulfate on iron and phosphate parameters in patients with iron deficiency and CKD: A randomized trial. *Clin J Am Soc Nephrol.* 2020;15:1251–1258. https://doi.org/10.2215/CJN.15291219. [PubMed: 32694162]

66. Cozzolino M, Ketteler M, Wagner CA. An expert update on novel therapeutic targets for hyperphosphatemia in chronic kidney disease: Preclinical and clinical innovations. *Expert Opin Ther Targets*. 2020;24:477–488. https://doi.org/10.1080/14728222.2020.1743680. [PubMed: 32191548]

67. Ketteler M, Wiecek A, Rosenkranz AR, Pasch A, Rekowski J, Hellmann B, et al. Efficacy and safety of a novel nicotinamide modified-release formulation in the treatment of refractory hyperphosphatemia in patients receiving hemodialysis—A randomized clinical trial. *Kidney Int Rep.* 2021;6:594–604. https://doi.org/10.1016/j.ekir.2020.12.012. [PubMed: 33732974]

68. Lenglet A, Liabeuf S, El Esper N, Brisset S, Mansour J, Lemaire-Hurtel AS, et al. Efficacy and safety of nicotinamide in haemodialysis patients: The NICOREN study. *Nephrol Dial Transplant*. 2017;32:870–879. https://doi.org/10.1093/ndt/gfw042. [PubMed: 27190329]

69. Pergola PE, Rosenbaum DP, Yang Y, Chertow GM. A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). *J Am Soc Nephrol.* 2021;32:1465–1473. https://doi.org/10.1681/ASN.2020101398. [PubMed: 33766811]

70. Akizawa T, Sato Y, Ikejiri K, Kanda H, Fukagawa M. Effect of tenapanor on phosphate binder pill burden in hemodialysis patients. *Kidney Int Rep.* 2021;6:2371–2380. https://doi.org/10.1016/j.ekir.2021.06.030. [PubMed: 34514198]

71. Sprague SM, Martin KJ, Coyne DW. Phosphate balance and CKD–mineral bone disease. *Kidney Int Rep.* 2021;6:2049–2058. https://doi.org/10.1016/j.ekir.2021.05.012. [PubMed: 34386654]

72. Moazzam AA, Boongird S. Ingestion of lanthanum carbonate tablets. *Am J Kidney Dis.* 2013;62:844. https://doi.org/10.1053/j.ajkd.2013.06.019. [PubMed: 23891360]

73. Wan LY, Zhang YQ, Chen MD, Liu CB, Wu JF. Relationship of structure and function of DNA-binding domain in vitamin D receptor. *Molecules*. 2015;20:12389–12399. https://doi.org/10.3390/molecules200712389. [PubMed: 26198224]

74. Bailie GR, Johnson CA. Comparative review of the pharmacokinetics of vitamin D analogues. *Semin Dial.* 2002;15:352–357. [PubMed: 12358640]

75. Zemplar Capsules Package Insert. AbbVie, Inc. North Chicago, IL. 2018.

76. Hectorol Injection. Package Insert. Genzyme Corporation, Cambridge, MA 2018.

77. Zheng Z, Shi H Fau - Jia J, Jia J Fau - Li D, Li D, Fau - Lin S, Lin S, Nephrol BMC. Vitamin D supplementation and mortality risk in chronic kidney disease: A meta-analysis of 20 observational studies. *BMC Nephrol.* 2013;14:199. [PubMed: 24066946]

78. Lu RJ, Zhu SM, Tang FL, Zhu XS, Fan ZD, Wang GL, et al. Effects of vitamin D or its analogues on the mortality of patients with chronic kidney disease: An updated systematic review and meta-analysis. *Eur J Clin Nutr.* 2017;71:683–693. https://doi.org/10.1038/ejcn.2017.59. [PubMed: 28488689]

79. Kandula P, Dobre M, Schold JD, Schreiber MJ Jr., Mehrotra R, Navaneethan SD. Vitamin D supplementation in chronic kidney disease: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol.* 2011;6:50–62. https://doi.org/10.2215/cjn.03940510. [PubMed: 20876671]

80. Sprague SM, Strugnell SA, Bishop CW. Extended-release calcifediol for secondary hyperparathyroidism in stage 3-4 chronic kidney disease. *Expert Rev Endocrinol Metab.* 2017;12:289–301. https://doi.org/10.1080/17446651.2017.1347501. [PubMed: 30058895]

81. Melamed ML, Chonchol M, Gutierrez OM, Kalantar-Zadeh K, Kendrick J, Norris K, et al. The role of vitamin D in CKD stages 3 to 4: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. *Am J Kidney Dis.* 2018;72:834–845. https://doi.org/10.1053/j.ajkd.2018.06.031. [PubMed: 30297082]

82. Harada K, Fujioka A, Konno M, Inoue A, Yamada H, Hirota Y. Pharmacology of Parsabiv((R)) (etelcalcetide, ONO-5163/AMG 416), a novel allosteric modulator of the calcium-sensing receptor, for secondary hyperparathyroidism in hemodialysis patients. *Eur J Pharmacol.* 2019;842:139–145. https://doi.org/10.1016/j.ejphar.2018.10.021. [PubMed: 30342948]

83. Sensipar (cinacalcet HCl) Tablets Package Insert. Amgen Inc., Thousand Oaks, CA 2019.

84. Parsabiv (etelcalcetide) Injection Package Insert. Amgen Inc., Thousand Oaks, CA 2021.

85. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, et al. The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transpl.* 2011;26:1327–1339. https://doi.org/10.1093/ndt/gfq725.

86. Block GA, Zaun D, Smits G, Persky M, Brillhart S, Nieman K, et al. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int.* 2010;78:578–589. https://doi.org/10.1038/ki.2010.167. [PubMed: 20555319]

87. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med.* 2012;367:2482–2494. https://doi.org/10.1056/NEJMoa1205624. [PubMed: 23121374]

88. Bover J, Urena P, Ruiz-Garcia C, daSilva I, Lescano P, del Carpio J, et al. Clinical and practical use of calcimimetics in dialysis patients with secondary hyperparathyroidism. *Clin J Am Soc Nephrol.* 2016;11:161–174. https://doi.org/10.2215/cjn.01760215. [PubMed: 26224878]

89. Block GA, Chertow GM, Cooper K, Xing S, Fouqueray B, Halperin M, et al. Fibroblast growth factor 23 as a risk factor for cardiovascular events and mortality in patients in the EVOLVE trial. *Hemodial Int.* 2021;25:78–85. https://doi.org/10.1111/hdi.12887. [PubMed: 33016505]

90. Floege J, Tsirtsonis K, Iles J, Drueke TB, Chertow GM, Parfrey P. Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial. *Kidney Int.* 2018;93:1475–1482. https://doi.org/10.1016/j.kint.2017.12.014. [PubMed: 29525393]

91. Block GA, Bushinsky DA, Cunningham J, Drueke TB, Ketteler M, Kewalramani R, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: Two randomized clinical trials. *JAMA.* 2017;317:146–155. https://doi.org/10.1001/jama.2016.19456. [PubMed: 28097355]

92. Karaboyas A, Muenz D, Fuller DS, Desai P, Lin T-C, Robinson BM, et al. Etelcalcetide utilization, dosing titration, and chronic kidney disease–mineral and bone disease (CKD-MBD): Marker responses in US hemodialysis patients. *Am J Kidney Dis.* 2021. https://doi.org/10.1053/j.ajkd.2021.05.020.

93. Bushinsky DA, Chertow GM, Cheng S, Deng H, Kopyt N, Martin KJ, et al. One-year safety and efficacy of intravenous etelcalcetide in patients on hemodialysis with secondary hyperparathyroidism. *Nephrol Dial Transplant*. 2020;35:1769–1778. https://doi.org/10.1093/ndt/gfz039. [PubMed: 30859218]

94. Friedl C, Zitt E. Role of etelcalcetide in the management of secondary hyperparathyroidism in hemodialysis patients: A review on current data and place in therapy. *Drug Des Devel Ther.* 2018;12:1589–1598. https://doi.org/10.2147/dddt.s134103. [PubMed: 29910605]

95. Wolf M, Block GA, Chertow GM, Cooper K, Fouqueray B, Moe SM, et al. Effects of etelcalcetide on fibroblast growth factor 23 in patients with secondary hyperparathyroidism receiving hemodialysis. *Clin Kidney J.* 2019;13:75–84. https://doi.org/10.1093/ckj/sfz034. [PubMed: 32082556]

96. Dörr K, Kammer M, Reindl-Schwaighofer R, Lorenz M, Prikoszovich T, Marculescu R, et al. Randomized trial of etelcalcetide for cardiac hypertrophy in hemodialysis. *Circ Res.* 2021;128:1616–1625. https://doi.org/10.1161/CIRCRESAHA.120.318556. [PubMed: 33825489]

97. Block GA, Bushinsky DA, Cheng S, Cunningham J, Dehmel B, Drueke TB, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: A randomized clinical trial. *JAMA.* 2017;317:156–164. https://doi.org/10.1001/jama.2016.19468. [PubMed: 28097356]

98. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular disease in chronic kidney disease: Pathophysiological insights and therapeutic options. *Circulation.* 2021;1157–1172. https://doi.org/10.1161/CIRCULATIONAHA.120.050686.

99. Ardhanari S, Alpert MA, Aggarwal K. Cardiovascular disease in chronic kidney disease: Risk factors, pathogenesis, and prevention. *Adv Perit Dial.* 2014;30:40–53. [PubMed: 25338421]

100. 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.

101. Goicoechea M, de Vinuesa SG, Quiroga B, Verde E, Bernis C, Morales E, et al. Aspirin for primary prevention of cardiovascular disease and renal disease progression in chronic kidney disease patients: A Multicenter Randomized Clinical Trial (AASER Study). *Cardiovasc Drugs Ther.* 2018;32:255–263. https://doi.org/10.1007/s10557-018-6802-1. [PubMed: 29943364]

102. Pallikadavath S, Ashton L, Brunskill NJ, Burton JO, Gray LJ, Major RW. Aspirin for the primary prevention of cardiovascular disease in individuals with chronic kidney disease: A systematic review and meta-analysis. *Eur J Prev Cardiol.* 2021. https://doi.org/10.1093/eurjpc/zwab132.

103. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Antiplatelet agents for chronic kidney disease. *Cochrane Database Syst Rev.* 2013:Cd008834. https://doi.org/10.1002/14651858.CD008834.pub2.

104. Noels H, Lehrke M, Vanholder R, Jankowski J. Lipoproteins and fatty acids in chronic kidney disease: Molecular and metabolic alterations. *Nat Rev Nephrol.* 2021;17:528–542. https://doi.org/10.1038/s41581-021-00423-5. [PubMed: 33972752]

105. Mathew RO, Rosenson RS, Lyubarova R, Chaudhry R, Costa SP, Bangalore S, et al. Concepts and controversies: Lipid management in patients with chronic kidney disease. *Cardiovasc Drugs Ther.* 2021;35:479–489. https://doi.org/10.1007/s10557-020-07020-x. [PubMed: 32556851]

106. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl.* 2013;3:259–305.

107. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192. https://doi.org/10.1016/S0140-6736(11)60739-3. [PubMed: 21663949]

108. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU, et al. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev.* 2013;9:CD004289. https://doi.org/10.1002/14651858.CD004289.pub5.

109. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2014;5:CD007784. https://doi.org/10.1002/14651858.CD007784.pub2.

110. Ali S, Dave N, Virani SS, Navaneethan SD. Primary and secondary prevention of cardiovascular disease in patients with chronic kidney disease. *Curr Atheroscler Rep.* 2019;21:32. https://doi.org/10.1007/s11883-019-0794-6. [PubMed: 31230129]

111. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73:e285–e350. https://doi.org/10.1016/j.jacc.2018.11.003. [PubMed: 30423393]

112. Rayner HC, Larkina M, Wang M, Graham-Brown M, van der Veer SN, Ecder T, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol.* 2017;12:2000–2007. https://doi.org/10.2215/CJN.03280317. [PubMed: 28923831]

113. Makar M, Smyth B, Brennan F. Chronic kidney disease-associated pruritus: A review. *Kidney Blood Press Res.* 2021:1–11. https://doi.org/10.1159/000518391.

114. Verduzco HA, Shirazian S. CKD-associated pruritus: New insights into diagnosis, pathogenesis, and management. *Kidney Int Rep.* 2020;5:1387–1402. https://doi.org/10.1016/j.ekir.2020.04.027. [PubMed: 32954065]

115. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med.* 2020;382:222–232. https://doi.org/10.1056/nejmoa1912770. [PubMed: 31702883]

116. Lipman ZM, Yosipovitch G. An evaluation of difelikefalin as a treatment option for moderate-to-severe pruritus in end stage renal disease. *Expert Opin Pharmacother.* 2021;22:549–555. https://doi.org/10.1080/14656566.2020.1849142. [PubMed: 33190563]

SELF-ASSESSMENT QUESTIONS

1. Which laboratory abnormalities are indicative of the secondary complications likely to occur in a patient with advanced CKD (stages G5 and ESKD)? *Decreases and increases are compared to the normal range for each parameter.*

   A. Increased phosphorus, potassium, active vitamin D

   B. Decreased bicarbonate, PTH, and potassium

   C. Increased PTH and bicarbonate; decreased active vitamin D

   D. Decreased phosphorus and PTH; increased potassium

   E. Decreased active vitamin D; increased PTH and potassium

2. Increased hepcidin levels observed in patients with CKD result in a/an _____ in iron release into plasma due to binding of hepcidin to _____?

   A. decrease; ferroportin

   B. increase; ferroportin

   C. decrease: unbound iron

   D. increase; unbound iron

   E. decrease; ferritin

3. Which IV iron agent is approved for higher dose administration and would allow an adult patient with CKD stage G5 to receive a total dose of 1 g at a single clinic visit?

   A. Ferric gluconate (Ferrlecit)

   B. Ferric derisomaltose (Monoferric)

   C. Iron sucrose (Venofer)

   D. Iron dextran (InFeD)

   E. Ferric pyrophosphate citrate (Triferic AVNU)

4. A 45-year-old male with CKD stage G3b (eGFR of 42 mL/min/1.73 m^2) is seen in the nephrology clinic. His labs today show the following: Hb 8.5 g/dL (85 g/L; 5.28 mmol/L) (down from 10.5 g/dL [105 g/L; 6.52 mmol/L] 3 months ago), TSat 34% (0.34), serum ferritin 610 ng/mL (µg/L; 13.7 pmol/L). He reports feeling tired and less able to do his activities of daily living. Work up shows no signs of active bleeding. Should this patient be started on an erythropoietic stimulating agent (ESA) and what is the rationale?

   A. Yes, his Hb is below 10 g/dL (100 g/L; 6.21 mmol/L) and the extent of decline indicates a high likelihood of needing a blood transfusion

   B. Yes, an ESA is indicated to enhance his quality of life and decrease mortality risk

   C. Yes, his Hb is below 12 g/dL (120 g/L; 7.45 mmol/L) and the goal is to normalize the Hb in non-dialysis CKD patients.

   D. No, an ESA will not be effective since his iron indices are low and iron should be administered first

   E. No, his Hb is above 8 g/dL (80 g/L; 4.97 mmol/L) and he has not had a large decline in Hb since his last visit

5. A patient with CKD stage G3b is to be started on oral ferrous sulfate for iron deficiency for at least 2 months. This patient should be instructed to take:

   A. A 325 mg test dose and be observed for anaphylactic reactions

   B. Iron between meals to increase absorption in the GI tract

   C. At least 500 mg of elemental iron per day if tolerated

   D. An antacid with iron to minimize the risk of GI adverse effects

   E. Ferrous sulfate with at least 8 ounces of water to prevent GI adverse effects

6. A patient with CKD stage G5 is noted to be iron deficient and is prescribed a full course of IV iron (1-1.5 g total). She will receive the total dose of IV iron divided over 2 clinic visits (today and one week later). Which regimen is most appropriate to administer at each visit?

   A. Ferumoxytol 510 mg IV push over 5 minutes

   B. Iron dextran 25 mg test dose followed by infusion of 500 mg over 30 minutes

   C. Ferric carboxymaltose 750 mg infused over 30 minutes

   D. Ferric gluconate 500 mg infused over 30 minutes

   E. Iron sucrose 1 gram administered over 3 hours

7. Which statement provides an accurate description of an available erythropoiesis stimulating agent and the advantage of using this agent.

   A. Epoetin-alfa-epbx has a longer half-life than darbepoetin alfa and requires less-frequent dosing.

   B. Darbepoetin alfa has a longer half-life than methoxy PEG beta and requires less-frequent dosing.

   C. Darbepoetin alfa has a shorter half-life than epoetin-alfa and requires more frequent dosing.

   D. Methoxy PEG epoetin-beta has a longer half-life than epoetin-alfa and requires less-frequent dosing.

   E. Methoxy PEG epoetin-beta may be used in a fixed dose and does not require dose titration.

8. Which of the following agents would be preferred in a hemodialysis patient with ESKD, a PTH persistently above 700 pg/mL (ng/L; 75 pmol/L) and elevated calcium levels?

   A. Etelcalcetide

   B. Cholecalciferol

   C. Calcitriol

   D. Ergocalciferol

   E. Calcifediol

9. A patient with ESKD on hemodialysis (HD) has had a PTH of 500 pg/mL (ng/L; 54 pmol/L) for the past 3 months, a phosphorus of 7.4 mg/dL (2.39 mmol/L), a calcium of 9.8 mg/dL (2.45 mmol/L), and an albumin of 3 g/dL (30 g/L). She currently receives calcitriol 1 µg IV three times weekly with HD, calcium acetate 1334 mg three times daily with meals, and ergocalciferol 50,000 IU once weekly. Which of the following is most appropriate to control her CKD-MBD?

   A. Discontinue the calcium acetate and begin a two-month course of aluminum hydroxide with meals

B. Increase the calcium acetate to 2001 mg with meals

C. Increase the calcitriol dose to 1.5 µg IV three times weekly

D. Change the calcium acetate to calcium carbonate

E. Discontinue the calcium acetate and begin lanthanum carbonate

10. Which vitamin D agent is active as given and is most appropriate for a patient with ESKD requiring vitamin D to treat secondary hyperparathyroidism (PTH 800 pg/mL [ng/L; 86 pmol/L])?

A. Ergocalciferol

B. Cholecalciferol

C. Calcifediol

D. Calcitriol

E. 1-α Hydroxylase

11. Which of the following is a potential advantage of using ferric citrate as a phosphate-binding agent compared to other sevelamer carbonate in a non-dialysis CKD patient?

A. It is available in a powder formulation.

B. It is also approved for iron-deficiency anemia.

C. It is available as a chewable tablet.

D. It can be given intravenously or orally.

E. It does not cause stool discoloration.

12. Which strategy should be followed when converting a patient from cinacalcet to etelcalcitide?

A. The two therapies should overlap by 2 weeks to allow etelcalcitide time to reach steady state.

B. Wait at least 7 days after discontinuing cinacalcet prior to initiating etelcalcitide.

C. Wait at least 4 weeks after discontinuing etelcalcitide prior to initiating cinacalcet.

D. Cinacalcet may be initiated once etelcalcitide levels are undetectable.

E. A test dose of etelcalcitide should be administered to determine if the patient will tolerate therapy.

13. According to KDIGO guidelines, statin therapy is recommended for primary prevention of cardiovascular events in which of the following patients?

A. 60-year-old male with ESKD not previously on a statin.

B. 75-year-old female with ESKD and diabetes not previously on a statin.

C. 40-year-old male with CKD G3b with coronary artery disease.

D. 38-year-old female with CKD G2 and no cardiac risk factors.

E. Statins are recommended only for secondary prevention in patients with CKD.

14. Which statement most accurately describes what is known regarding cardiovascular disease (CVD) in patients with CKD?

    A. There is a lower risk of CVD once a patient begins hemodialysis.

    B. In general, survival is the same for a given CVD condition compared to patients without CKD.

    C. Nontraditional risk factors for CVD in patients with CKD include proteinuria and anemia.

    D. The prevalence of CVD decreases as CKD progresses from early- to later-stage CKD.

    E. There is an abundance of evidence-based data to address treatment for most. cardiovascular diseases in patients with CKD since they are often included in the clinical trials.

15. Which is the most evidence-based treatment strategy for a patient with ESKD experiencing chronic CKD-associated pruritis?

    A. Difelikefalin to target kappa opioid receptors

    B. Paricalcitol to reduce parathyroid hormone to goal levels

    C. More frequent dialysis to remove histamine

    D. Diphenhydramine to inhibit histamine-induced allergic symptoms

    E. Topical corticosteroid therapy

SELF-ASSESSMENT QUESTION-ANSWERS

1. **E.** Common secondary complications beyond the main complications discussed in this chapter are listed in Table 63-1. Among them, choice is the only one that includes laboratory abnormalities consistent with advanced CKD. Decreased levels of active vitamin D and increased PTH are consistent with CKD-MBD (increased phosphorus is also anticipated). Hyperkalemia is also expected in a patient with advanced CKD. Other complications include anemia (indicated by a decreased hemoglobin) and metabolic acidosis (indicated by a decrease serum bicarbonate).

2. **A.** Hepcidin is a hormone produced in the liver and is the primary regulator of iron homeostasis. This hormone binds to and inhibits ferroportin that transports iron out of storage cells and into the circulation. Hepcidin levels are increased in patients with CKD and lead to decreased intestinal iron absorption, impaired iron recycling from macrophages, and decreased mobilization from hepatocytes.

3. **B.** Among the agents listed, ferric derisomaltose is the only agent approved for higher dose administration in patient with nondialysis CKD and offers the advantage of administering a full course of iron (1,000 mg) in one administration (see Table 63-4).

4. **A.** This patient meets the criteria for initiation of an ESA (Table 63-2) based on his currently Hb level of less than 10 g/dL (100 g/L; 6.21 mmol/L) and the rate of decline in this patient's Hb indicating that a further decline is likely. The iron indices are at goal so additional iron supplementation alone is not expected to correct his anemia. Option A is consistent with the criteria listed in Table 63-2.

5. **B.** Taking iron on an empty and avoiding agents that increase the pH of the GI tract is recommended to improve iron absorption. A test dose is required only for intravenous therapy with iron dextran. Increased fluid intake is not expected to alter tolerability of oral iron.

6. **C.** When iron is administered intravenously the main consideration is to avoid giving iron too rapidly in order to avoid adverse reactions (eg, hypotension, iron overload). Iron formulations differ in terms of the carbohydrate shell that surrounds iron and the rate at which iron is released. Ferric carboxymaltose, ferric derisomaltose, and ferumoxytol and agents that may be administered in a larger dose and at a faster rate compared to the smaller molecular weight compounds (iron sucrose, sodium ferric gluconate, and iron dextran). Of the options listed, only choice C follows the recommendations for the amount and rate of administration (see Table 63-4).

7. **C.** Available ESAs and the corresponding half-life for each are listed in Table 63-5. Methoxy polyethylene glycol (PEG) epoetin-beta has the longest half life and offer the option of less-frequent dosing. The starting dose is a weight-based dose and the dose titration is dependent on the rate of change in hemoglobin as with other ESAs.

8. **A.** Based on the persistently elevated PTH values, this patient meets criteria for vitamin D therapy and/or a calcimimetics based on KDIGO guidelines (see Table 63-6). Since the patient has hypercalemia, the best option now is a calcimimetic which lowers both PTH and calcium. Etelcalcetide is the only calcimimetic agent listed (cinacalcet is the other available agent). Vitamin D, particularly calcitriol, and the vitamin D analogs may contribute further to hypercalcemia. Etelcalcetide is administered intravenously at the end of dialysis and is a good option if nonadherence is a concern. Cinacalcet is an oral calcimimetic that would also be an option, but patient adherence with therapy would have to be considered.

9. **E.** This patient has a PTH within the target range of 2 to 9 times the upper limit of normal (using a general upper limit of 65 pg/mL [ng/L; 7 pmol/L), an elevated phosphorus and a corrected calcium of 10.4 mg/dL (2.60 mmol/L) which is at the upper limit of normal. The patient should continue to receive vitamin D with calcitriol or a vitamin D analog since the PTH has been within the target range. A phosphate binder is required based on the phosphorus level, but a calcium-containing agent is not the best option given the high calcium levels. The best option is to minimize the risk of hypercalcemia by switching to a non-calcium containing agent such as lanthanum, iron-based binders, or sevelamer carbonate.

10. **D.** Calcitriol is the active form of vitamin D (1-25 dihydroxyvitamin D_3) and is the only agent on the list that is active as given. Ergocalciferol and cholecalciferol are nutritional vitamin D agents and require activation by the liver and the kidney. Calcifidiol is 25-hydroxvitamin D_3 (the precursor form of vitamin D) that requires activation by the liver. 1-α-Hydroxylase is not a vitamin D agent but is the enzyme responsible for converting vitamin D to the active form in the kidney.

11. **B.** Ferric citrate is an iron-containing phosphate binder approved for use as both a phosphate binder in patients with CKD receiving dialysis and for iron deficiency anemia in CKD patients not on dialysis. Clinical studies demonstrated a significant increase in iron indices (transferrin saturation and serum ferritin). This agent is only available in tablet form, not as a powder, and is not to be chewed. As an iron-containing agent, stool discoloration may occur.

12. **B.** If switching a patient from cinacalcet to etelcalcetide, then cinacalcet should be discontinued for at least 7 days prior to starting etelcalcetide. If switching patients from etelcalcetide to cinacalcet, etalcalcetide should be discontinued for at least 4 weeks prior to starting cinacalcet due to the long half-life of etalcalcetide.

13. **C.** Refer to the “Statins in CKD” section of the chapter and the KDIGO Lipid Guidelines. Options A and B are incorrect because adults with dialysis-dependent CKD should not be initiated on a statin. Option C is correct because adults aged 18 to 49 years not receiving dialysis should be initiated on a statin if they have known coronary artery disease. Option D is incorrect since this patient is not older 50 years and her eGFR is >60 mL/min/1.73 m^2 with no additional risk factors. Option E is incorrect as statins are indicated for primary prevention in certain types of CKD patients.

14. **C.** Proteinuria and anemia are among the nontraditional risk factors for cardiovascular disease in patients with advanced CKD. The other options are incorrect as patients with CKD have a higher mortality, have worsening risk of cardiovascular disease as kidney function declines, and have a higher mortality compared to patients without CKD. Most clinical trials exclude patients with advanced CKD and there is limited data for most cardiovascular diseases in this population.

15. **A.** The mechanism of CKD-associated pruritus is poorly understood. Pruritus has been associated with inadequate dialysis and elevated PTH, calcium, and phosphorus; however, these associations are inconsistent and their correction does not necessarily correlate with resolution of pruritus. Difelikefalin is a peripheral kappa opioid receptor agonist exerts antipruritic effects by means of activation of kappa opioid receptors on peripheral neurons and immune cells. This agent has been studied in HD patients and was approved for moderate-to-severe pruritus in hemodialysis patients.