GUIDELINE 1. DEFINITION AND STAGES OF CHRONIC KIDNEY DISEASE

Adverse outcomes of chronic kidney disease (CKD) can often be prevented or delayed through early detection and treatment. Earlier stages of chronic kidney disease can be detected through routine laboratory measurements.

- The presence of chronic kidney disease should be established, based on presence of kidney damage and level of kidney function (glomerular filtration rate [GFR]), irrespective of diagnosis.
- Among patients with chronic kidney disease, the stage of disease should be assigned based on the level of kidney function, irrespective of diagnosis, according to the KDOQI CKD classification.

*CKD is defined as either kidney damage or GFR < 60 mL/min/1.73 m² for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging.

## Stage of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or T GFR</td>
<td>≥60</td>
<td>Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
<td>Estimating progression</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
<td>Evaluating and treating complications</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
<td>Preparation for kidney replacement therapy</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (or dialysis)</td>
<td>&lt;15</td>
<td>Replacement (if uremia present)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

*Includes actions from preceding stages.

Abbreviations: CVD, cardiovascular disease

GUIDELINE 2. EVALUATION AND TREATMENT

The evaluation and treatment of patients with chronic kidney disease requires understanding of separate but related concepts of diagnosis, comorbid conditions, severity of disease, complications of disease, and risks for loss of kidney function and cardiovascular disease.

- Patients with chronic kidney disease should be evaluated to determine:
  - Diagnosis (type of kidney disease);
  - Comorbid conditions;
  - Severity, assessed by level of kidney function;
  - Complications, related to level of kidney function;
  - Risk for loss of kidney function;
  - Risk for cardiovascular disease.

- Treatment of chronic kidney disease should include:
  - Specific therapy, based on diagnosis;
  - Evaluation and management of comorbid conditions;
  - Slowing the loss of kidney function;
  - Prevention and treatment of cardiovascular disease;
  - Prevention and treatment of complications of decreased kidney function;
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- Preparation for kidney failure and kidney replacement therapy;
- Replacement of kidney function by dialysis and transplantation, if signs and symptoms of uremia are present.

- A clinical action plan should be developed for each patient, based on the stage of disease as defined by the KDOQI CKD classification (see Table 33).

- Review of medications should be performed at all visits for the following:
  - Dosage adjustment based on level of kidney function;
  - Detection of potentially adverse effects on kidney function or complications of chronic kidney disease;
  - Detection of drug interactions;
  - Therapeutic drug monitoring, if possible.

- Self-management behaviors should be incorporated into the treatment plan at all stages of chronic kidney disease.

- Patients with chronic kidney disease should be referred to a specialist for consultation and co-management if the clinical action plan cannot be prepared, the prescribed evaluation of the patient cannot be carried out, or the recommended treatment cannot be carried out. In general, patients with GFR <30 mL/min/1.73 m² should be referred to a nephrologist.

GUIDELINE 3. INDIVIDUALS AT INCREASED RISK OF CHRONIC KIDNEY DISEASE

Some individuals without kidney damage and with normal or elevated GFR are at increased risk for development of chronic kidney disease.

- All individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk of developing chronic kidney disease, based on clinical and sociodemographic factors.

- Individuals at increased risk of developing chronic kidney disease should undergo testing for markers of kidney damage, and to estimate the level of GFR.

- Individuals found to have chronic kidney disease should be evaluated and treated as specified in Guideline 2.

- Individuals at increased risk, but found not to have chronic kidney disease, should be advised to follow a program of risk factor reduction, if appropriate, and undergo repeat periodic evaluation.

GUIDELINE 4. ESTIMATION OF GFR

Estimates of GFR are the best overall indices of the level of kidney function.

The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size.

The following equations provide useful estimates of GFR:

- In adults, the MDRD Study and Cockcroft-Gault equations
- In children, the Schwartz and Counahan-Barratt equations.

- The serum creatinine concentration alone should not be used to assess the level of kidney function.

- Clinical laboratories should report an estimate of GFR using a prediction equation, in addition to reporting the serum creatinine measurement.

- Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard.

Measurements of creatinine clearance using timed (for example, 24-hour) urine collections do not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for:

- Estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting);
Estimating Renal Function

**GUIDELINE 5. ASSESSMENT OF PROTEINURIA**
Normal individuals usually excrete very small amounts of protein in the urine. Persistently increased protein excretion is usually a marker of kidney damage. The excretion of specific types of protein, such as albumin or low molecular weight globulins, depends on the type of kidney disease that is present. Increased excretion of albumin is a sensitive marker for chronic kidney disease due to diabetes, glomerular disease, and hypertension. Increased excretion of low molecular weight globulins is a sensitive marker for some types of tubulointerstitial disease. In this guideline, the term “proteinuria” refers to increased urinary excretion of albumin, other specific proteins, or total protein; “albuminuria” refers specifically to increased urinary excretion of albumin. “Microalbuminuria” refers to albumin excretion above the normal range but below the level of detection by tests for total protein. Guidelines for detection and monitoring of proteinuria in adults and children differ because of differences in the prevalence and type of chronic kidney disease.

Guidelines for Adults and Children
- Under most circumstances, untimed (“spot”) urine samples should be used to detect and monitor proteinuria in children and adults.
- It is usually not necessary to obtain a timed urine collection (overnight or 24-hour) for these evaluations in either children or adults.
- First morning specimens are preferred, but random specimens are acceptable if first morning specimens are not available.
- In most cases, screening with urine dipsticks is acceptable for detecting proteinuria:
  - Standard urine dipsticks are acceptable for detecting increased total urine protein.
• Albumin-specific dipsticks are acceptable for detecting albuminuria.

- Patients with a positive dipstick test (1+ or greater) should undergo confirmation of proteinuria by a quantitative measurement (protein-to-creatinine ratio or albumin-to-creatinine ratio) within 3 months.
- Patients with two or more positive quantitative tests temporally spaced by 1 to 2 weeks should be diagnosed as having persistent proteinuria and undergo further evaluation and management for chronic kidney disease as stated in Guideline 2.
- Monitoring proteinuria in patients with chronic kidney disease should be performed using quantitative measurements.

Specific Guidelines for Adults
- When screening adults at increased risk for chronic kidney disease, albumin should be measured in a spot urine sample using either:
  o Albumin-specific dipstick;
  o Albumin-to-creatinine ratio.

- When monitoring proteinuria in adults with chronic kidney disease, the protein-to-creatinine ratio in spot urine samples should be measured using:
  o Albumin-to-creatinine ratio;
  o Total protein-to-creatinine ratio is acceptable if albumin-to-creatinine ratio is high (>500 to 1,000 mg/g).

GUIDELINE 6. MARKERS OF CHRONIC KIDNEY DISEASE OTHER THAN PROTEINURIA
Markers of kidney damage in addition to proteinuria include abnormalities in the urine sediment and abnormalities on imaging studies. Constellations of markers define clinical presentations for some types of chronic kidney disease. New markers are needed to detect kidney damage that occurs prior to a reduction in GFR in other types of chronic kidney diseases.

- Urine sediment examination or dipstick for red blood cells and white blood cells should be performed in patients with chronic kidney disease and in individuals at increased risk of developing chronic kidney disease.
- Imaging studies of the kidneys should be performed in patients with chronic kidney disease and in selected individuals at increased risk of developing chronic kidney disease.
- Although several novel urinary markers (such as tubular or low-molecular weight proteins and specific mononuclear cells) show promise of future utility, they should not be used for clinical decision-making at present.

GUIDELINE 7. ASSOCIATION OF LEVEL OF GFR WITH HYPERTENSION
High blood pressure is both a cause and a complication of chronic kidney disease. As a complication, high blood pressure may develop early during the course of chronic kidney disease and is associated with adverse outcomes—in particular, faster loss of kidney function and development of cardiovascular disease.

- Blood pressure should be closely monitored in all patients with chronic kidney disease.
- Treatment of high blood pressure in chronic kidney disease should include specification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease (Guideline 13) and development of cardiovascular disease (Guideline 15).

GUIDELINE 8. ASSOCIATION OF LEVEL OF GFR WITH ANEMIA
Anemia usually develops during the course of chronic kidney disease and may be associated with adverse outcomes.
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- Patients with GFR <60 mL/min/1.73 m² should be evaluated for anemia. The evaluation should include measurement of hemoglobin level.
- Anemia in chronic kidney disease should be evaluated and treated.

**GUIDELINE 9. ASSOCIATION OF LEVEL OF GFR WITH NUTRITIONAL STATUS**

Protein energy malnutrition develops during the course of chronic kidney disease and is associated with adverse outcomes. Low protein and calorie intake is an important cause of malnutrition in chronic kidney disease.

- Patients with GFR <60 mL/min/1.73 m² should undergo assessment of dietary protein and energy intake and nutritional status—see K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (CRF), Guidelines 23 and 26:
  - Guideline 23. Panels of Nutritional Measures for Nondialyzed Patients: "For individuals with CRF (GFR <20 mL/min) protein-energy nutritional status should be evaluated by serial measurements of a panel of markers including at least one value from each of the following clusters:
    1. Serum albumin;
    2. Edema-free actual body weight, percent standard (NHANES II) body weight, or subjective global assessment (SGA); and
    3. Normalized protein nitrogen appearance (nPNA) or dietary interviews and diaries. (Evidence and Opinion)"
- Guideline 26. Intensive Nutritional Counseling for Chronic Renal Failure: "The nutritional status of individuals with CRF should be monitored at regular intervals."
- Patients with decreased dietary intake or malnutrition should undergo dietary modification, counseling, and education or specialized nutrition therapy—see K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (CRF), Guidelines 24 and 25:
  - Guideline 24. Dietary Protein Intake for Nondialyzed Patients: "For individuals with chronic renal failure (GFR <25 mL/min) who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.60 g protein/kg/d should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate dietary energy intake with such a diet, an intake of up to 0.75 g protein/kg/d may be prescribed. (Evidence and Opinion)."
  - Guideline 25. Dietary Energy Intake (DEI) for Nondialyzed Patients: "The recommended DEI for individuals with chronic renal failure (GFR <25 mL/min) who are not undergoing maintenance dialysis is 35 kcal/kg/d for those who are younger than 60 years old and 30-35 kcal/kg/d for individuals who are 60 years of age or older. (Evidence and Opinion)."

**GUIDELINE 10. ASSOCIATION OF LEVEL OF GFR WITH BONE DISEASE AND DISORDERS OF CALCIUM AND PHOSPHORUS METABOLISM**

Bone disease and disorders of calcium and phosphorus metabolism develop during the course of chronic kidney disease and are associated with adverse outcomes.

- Patients with GFR <60 mL/min/1.73 m² should be evaluated for bone disease and disorders of calcium and phosphorus metabolism.
- Patients with bone disease and disorders of bone metabolism should be evaluated and treated.

**GUIDELINE 11. ASSOCIATION OF LEVEL OF GFR WITH NEUROPATHY**

Neuropathy develops during the course of chronic kidney disease and may become symptomatic.

- Patients with chronic kidney disease should be periodically assessed for central and peripheral neurologic involvement by eliciting symptoms and signs during routine office visits or exams.
- Specialized laboratory testing for neuropathy in patients with chronic kidney disease is indicated only in the presence of symptoms.
GUIDELINE 12. ASSOCIATION OF LEVEL OF GFR WITH INDICES OF FUNCTIONING AND WELL-BEING
Impairments in domains of functioning and well-being develop during the course of chronic kidney disease and are associated with adverse outcomes. Impaired functioning and well-being may be related to sociodemographic factors, conditions causing chronic kidney disease, complications of kidney disease, or possibly directly due to reduced GFR.
  - Patients with GFR <60 mL/min/1.73 m2 should undergo regular assessment for impairment of functioning and well-being:
    - To establish a baseline and monitor changes in functioning and well-being over time
    - To assess the effect of interventions on functioning and well-being.

GUIDELINE 13. FACTORS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION IN CHRONIC KIDNEY DISEASE
The level of kidney function tends to decline progressively over time in most patients with chronic kidney diseases.
  - The rate of GFR decline should be assessed in patients with chronic kidney disease to:
    - Predict the interval until the onset of kidney failure;
    - Assess the effect of interventions to slow the GFR decline.
  - Among patients with chronic kidney disease, the rate of GFR decline should be estimated by:
    - Computing the GFR decline from past and ongoing measurements of serum creatinine;
    - Ascertaining risk factors for faster versus slower GFR decline, including type (diagnosis) of kidney disease, nonmodifiable and modifiable factors.
  - Interventions to slow the progression of kidney disease should be considered in all patients with chronic kidney disease.
    - Interventions that have been proven to be effective include:
      - Strict glucose control in diabetes;
      - Strict blood pressure control;
      - Angiotensin-converting enzyme inhibition or angiotensin-2 receptor blockade.
    - Interventions that have been studied, but the results are inconclusive, include:
      - Dietary protein restriction;
      - Lipid-lowering therapy;
      - Partial correction of anemia.
  - Attempts should be made to prevent and correct acute decline in GFR. Frequent causes of acute decline in GFR include:
    - Volume depletion;
    - Intravenous radiographic contrast;
    - Selected antimicrobial agents (for example, aminoglycosides and amphotericin B);
    - Nonsteroidal anti-inflammatory agents, including cyclo-oxygenase type 2 inhibitors;
    - Angiotensin-converting enzyme inhibition and angiotensin-2 receptor blockers;
    - Cyclosporine and tacrolimus;
    - Obstruction of the urinary tract.
  - Measurements of serum creatinine for estimation of GFR should be obtained at least yearly in patients with chronic kidney disease, and more often in patients with:
    - GFR <60 mL/min/1.73 m2;
    - Fast GFR decline in the past (4 mL/min/1.73 m2 per year);
    - Risk factors for faster progression;
    - Ongoing treatment to slow progression;
    - Exposure to risk factors for acute GFR decline.
GUIDELINE 14. ASSOCIATION OF CHRONIC KIDNEY DISEASE WITH DIABETIC COMPLICATIONS
The risk of cardiovascular disease, retinopathy, and other diabetic complications is higher in patients with diabetic kidney disease than in diabetic patients without kidney disease.

- Prevention, detection, evaluation, and treatment of diabetic complications in patients with chronic kidney disease should follow published guidelines and position statements.
- Guidelines regarding angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and strict blood pressure control are particularly important since these agents may prevent or delay some of the adverse outcomes of both kidney and cardiovascular disease.
- Application of published guidelines to diabetic patients with chronic kidney disease should take into account their “higher-risk” status for diabetic complications.

GUIDELINE 15. ASSOCIATION OF CHRONIC KIDNEY DISEASE WITH CARDIOVASCULAR DISEASE
Patients with chronic kidney disease, irrespective of diagnosis, are at increased risk of cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. Both “traditional” and “chronic kidney disease related (nontraditional)” CVD risk factors may contribute to this increased risk.

- All patients with chronic kidney disease should be considered in the “highest risk” group for cardiovascular disease, irrespective of levels of traditional CVD risk factors.
- All patients with chronic kidney disease should undergo assessment of CVD risk factors, including:
  - Measurement of “traditional” CVD risk factors in all patients;
  - Individual decision-making regarding measurement of selected “CKD-related” CVD risk factors in some patients.
- Recommendations for CVD risk factor reduction should take into account the “highest-risk” status of patients with chronic kidney disease.
GUIDELINE 1. EVALUATION OF CALCIUM AND PHOSPHORUS METABOLISM

1.1 Serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH) should be measured in all patients with CKD and GFR <60 mL/min/1.73 m². (EVIDENCE) The frequency of these measurements should be based on the stage of chronic kidney disease (Table 14). (OPINION)

1.2 These measurements should be made more frequently if the patient is receiving concomitant therapy for the abnormalities in the serum levels of calcium, phosphorus or PTH, as detailed in Guidelines 4, 5, 7, and 8 and in transplant recipient, Guideline 16.

1.3 Measurement of plasma PTH levels may be done less frequently for those with levels within the low end of the target levels (Table 15). (OPINION)

1.4 The target range of plasma levels of intact PTH in the various stages of CKD are denoted in Table 15.

GUIDELINE 2. ASSESSMENT OF BONE DISEASE ASSOCIATED WITH CKD

2.1 The most accurate diagnostic test for determining the type of bone disease associated with CKD is iliac crest bone biopsy with double tetracycline labeling and bone histomorphometric analysis. (EVIDENCE)

2.2 It is not necessary to perform bone biopsy for most situations in clinical practice. However, a bone biopsy should be considered in patients with kidney failure (Stage 5) who have:

2.2a Fractures with minimal or no trauma (pathological fractures); (OPINION)

2.2b Intact plasma PTH levels between 100 and 500 pg/mL (11.0 to 55.0 pmol/L) (in CKD Stage 5) with coexisting conditions such as unexplained hypercalcemia, severe bone pain, or unexplained increases in bone alkaline phosphatase activity; (OPINION)

2.2c Suspected aluminum bone disease, based upon clinical symptoms or history of aluminum exposure. (OPINION) (See Guideline 11.)

2.3 Bone radiographs are not indicated for the assessment of bone disease of CKD, (EVIDENCE) but they are useful in detecting severe peripheral vascular calcification (OPINION) and bone disease due to β2-microglobulin amyloidosis. (See Guideline 10.) (EVIDENCE)

2.4 Bone mineral density (BMD) should be measured by dual energy X-ray absorptiometry (DEXA) in patients with fractures and in those with known risk factors for osteoporosis. (OPINION)
GUIDELINE 3. EVALUATION OF SERUM PHOSPHORUS LEVELS
3.1 In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (EVIDENCE) and no higher than 4.6 mg/dL (1.49 mmol/L). (OPINION)
3.2 In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L). (EVIDENCE)

GUIDELINE 4. RESTRICTION OF DIETARY PHOSPHORUS IN PATIENTS WITH CKD
4.1 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated (>4.6 mg/dL [1.49 mmol/L]) at Stages 3 and 4 of CKD, (OPINION) and >5.5 mg/dL (1.78 mmol/L) in those with kidney failure (Stage 5). (EVIDENCE)
4.2 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact PTH are elevated above target range of the CKD stage (see Table 15 in Guideline 1). (EVIDENCE)
4.3 The serum phosphorus levels should be monitored every month following the initiation of dietary phosphorus restriction. (OPINION)

GUIDELINE 5. USE OF PHOSPHATE BINDERS IN CKD
In CKD Patients (Stages 3 and 4):
5.1 If phosphorus or intact PTH levels cannot be controlled within the target range (see Guidelines 1, 3), despite dietary phosphorus restriction (See Guideline 4), phosphate binders should be prescribed. (OPINION)
5.2 Calcium-based phosphate binders are effective in lowering serum phosphorus levels (EVIDENCE) and may be used as the initial binder therapy. (OPINION)
In CKD Patients With Kidney Failure (Stage 5):
5.3 Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)
5.4 In dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents, a combination of both should be used. (OPINION)
5.5 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)
5.6 Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dL [2.54 mmol/L]), or whose plasma PTH levels are <150 pg/mL (16.5 pmol/L) on 2 consecutive measurements. (EVIDENCE)
5.7 Noncalcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. (OPINION)
5.8 In patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L), aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. (OPINION) In such patients, more frequent dialysis should also be considered. (EVIDENCE)

GUIDELINE 6. SERUM CALCIUM AND CALCIUM-PHOSPHORUS PRODUCT
In CKD Patients (Stages 3 and 4):
6.1 The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used. (EVIDENCE)

In CKD Patients With Kidney Failure (Stage 5):
6.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION)
6.3 In the event corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that cause serum calcium to rise should be adjusted as follows:
   6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a noncalcium-, nonaluminum-, nonmagnesium-containing phosphate binder. (OPINION) See Guideline 5.
   6.3b In patients taking active vitamin D sterols, the dose should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION) See Guideline 8B.
   6.3c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite modification of therapy with vitamin D and/or discontinuation of calcium-based phosphate binders, dialysis using low dialysate calcium (1.5 to 2.0 mEq/L) may be used for 3 to 4 weeks (OPINION) See Guideline 9.

6.4 Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day. (OPINION) See Guideline 5.
6.5 The serum calcium-phosphorus product should be maintained at <55 mg2/dL2. (EVIDENCE) This is best achieved by controlling serum levels of phosphorus within the target range. (OPINION) See Guidelines 3, 4, and 5.
6.6 Patients whose serum levels of corrected total calcium are below the lower limit for the laboratory used (<8.4 mg/dL [2.10 mmol/L]) should receive therapy to increase serum calcium levels if:
   6.6a There are clinical symptoms of hypocalcemia such as paresthesia, Chvostek’s and Trousseau’s signs, bronchospasm, laryngospasm, tetany, and/or seizures (OPINION); or
   6.6b The plasma intact PTH level is above the target range for the CKD Stage (See Table 15 in Guideline 1). (OPINION)
6.7 Therapy for hypocalcemia should include calcium salts such as calcium carbonate (EVIDENCE) and/or oral vitamin D sterols. (EVIDENCE) See Guideline 8B.

GUIDELINE 7. PREVENTION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND VITAMIN D DEFICIENCY IN CKD PATIENTS (ALGORITHM 1)
In CKD Patients (Stages 3 and 4):

7.1 If plasma intact PTH is above the target range for the stage of CKD (Table 15, Guideline 1) serum 25-hydroxyvitamin D should be measured at first encounter. If it is normal, repeat annually.

(EVIDENCE)
7.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL (75 nmol/L), supplementation with vitamin D2, (ergocalciferol) should be initiated (Table 26). (OPINION)

7.3 Following initiation of vitamin D therapy:
7.3a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus (Algorithm 1).
7.3b The serum levels of corrected total calcium and phosphorus should be measured at least every 3 months. (OPINION)
7.3c If the serum levels of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), discontinue ergocalciferol therapy and all forms of vitamin D therapy. (OPINION)
7.3d If the serum phosphorus exceeds 4.6 mg/dL (1.49 mmol/L), add or increase the dose of phosphate binder. (See Guidelines 4 and 5) If hyperphosphatemia persists, discontinue vitamin D therapy. (OPINION)
7.3e Once patients are replete with vitamin D, continued supplementation with a vitamin-D-containing multi-vitamin preparation should be used with annual reassessment of serum levels of 25-hydroxyvitamin D, and the continued assessment of corrected total calcium and phosphorus every 3 months. (OPINION)

In CKD Patients With Kidney Failure (Stage 5):
7.4 Therapy with an active vitamin D sterol (calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) should be provided if the plasma levels of intact PTH are > 300 g/mL. (OPINION) See Guideline 8B.

GUIDELINE 8. VITAMIN D THERAPY IN CKD PATIENTS
This Guideline encompasses 2 parts: Guideline 8A, which deals with active vitamin D sterol therapy in CKD Stages 3 and 4, and Guideline 8B, which deals with CKD Stage 5.

GUIDELINE 8A, ACTIVE VITAMIN D THERAPY IN PATIENTS WITH STAGES 3 AND 4 CKD (ALGORITHM 2)
8A.1 In patients with CKD Stages 3 and 4, therapy with an active oral vitamin D sterol (calcitriol, alfalcacidol, or doxercalciferol) is indicated when serum levels of 25(OH)-vitamin D are >30 ng/mL (75 nmol/L), and plasma levels of intact PTH are above the target range for the CKD stage (see Table 15, Guideline 1). (EVIDENCE) Initial doses are provided in Table 27.
8A.1a Treatment with an active vitamin D sterol should be undertaken only in patients with serum levels of corrected total calcium <9.5 mg/dL (2.37 mmol/L) and serum phosphorus <4.6 mg/dL (1.49 mmol/L). (OPINION)
8A.1b Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up. (OPINION)
8A.2 During therapy with vitamin D sterols, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter. (OPINION)
8A.3 Dosage adjustments for patients receiving active vitamin D sterol therapy should be made as follows:

8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage (Table 15, Guideline 1), hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)
8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to < 9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)
8A.3c If serum levels of phosphorus rise to > 4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy, initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to ≤ 4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol. (OPINION)

GUIDELINE 8B. VITAMIN D THERAPY IN PATIENTS ON DIALYSIS (CKD STAGE 5)
8B.1 Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL (33.0 pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol; see Table 28) to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL (16.5 to 33.0 pmol/L). (EVIDENCE)
8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE)
8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range (see Guidelines 3 and 6, respectively), a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (OPINION)
8B.2 When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved. (OPINION)
8B.3 For patients treated with peritoneal dialysis, oral doses of calcitriol (0.5 to 1.0 µg) or doxercalciferol (2.5 to 5.0 µg) can be given 2 or 3 times weekly. Alternatively, a lower dose of calcitriol (0.25 µg) may be administered daily. (OPINION)
8B.4 When either hemodialysis or peritoneal dialysis patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH. Each of these three variables is considered separately with suggested interventions based on the various values obtained in Algorithm 3, Algorithm 4, and Algorithm 5. (OPINION)
Algorithm 3. Managing Vitamin D sterols based on serum calcium levels.

Measure serum Ca

Ca > 10.2 mg/dL (2.54 mmol/L)

Stop vitamin D therapy

Ca < 9.5 mg/dL (2.37 mmol/L)

Reduce dose of Ca-containing phosphate binders and change to or increase dose of non-Ca phosphate binders

Ca 9.5-10.2 mg/dL (2.37-2.54 mmol/L)

Measure serum Ca

Ca > 10.2 mg/dL (2.54 mmol/L)

Continue or modify vitamin D using Algorithm 4 (Serum P) and Algorithm 5 (Serum PTH)

Ca < 9.5 mg/dL (2.37 mmol/L)

Measure serum PTH

Is serum PTH ≥ 300 pg/mL (33.0 pmol/L)?

Yes

OPTIONAL: Dialysate Ca 2.0 mEq/L for 2-3 HD Rx

OPTIONAL: Change to "less calcemic" vitamin D sterol

No

Continue or modify vitamin D using Algorithm 4 (Serum P) and Algorithm 5 (Serum PTH)
Algorithm 4. Managing Vitamin D sterols based on serum phosphorus levels.

Measure serum P

P >6.0 mg/dL (1.94 mmol/L) → Hold vitamin D therapy

P ≤ 6.0 mg/dL (1.94 mmol/L)

P > 5.5 mg/dL (1.78 mmol/L) → Increase phosphate binder dose

P ≤ 5.5 mg/dL (1.78 mmol/L)

Measure serum P

Is serum P < 5.5 mg/dL (1.78 mmol/L)?

No

Yes

In patient has been on vitamin D:
reduce dose by 25%-50%

If vitamin D has been held:
resume at dose lowered by 25%-50%

Continue or modify
vitamin D using
Algorithm 1 (Serum Ca) and Algorithm 5
(Serum PTH)
GUIDELINE 9. DIALYSATE CALCIUM CONCENTRATIONS

9.1 The dialysate calcium concentration in hemodialysis or peritoneal dialysis should be 2.5 meq/L (1.25 mmol/L). (OPINION)

9.2 Higher or lower dialysate calcium levels are indicated in selected patients. (OPINION)
GUIDEINE 10. β2-MICROGLOBULIN AMYLOIDOSIS
10.1 Screening for β2-microglobulin amyloidosis, including measurement of serum levels of β2-microglobulin, is not recommended. (OPINION)
   10.1a No currently available therapy (except kidney transplantation) can stop disease progression of β2-microglobulin amyloidosis or provide symptomatic relief. (EVIDENCE)
   10.1b Kidney transplant should be considered to stop disease progression or provide symptomatic relief in patients with β2-microglobulin amyloidosis. (EVIDENCE)
   10.1c In patients with evidence of, or at risk for, β2-microglobulin amyloidosis noncuprophane (EVIDENCE), high-flux dialyzers (OPINION) should be used.

GUIDELINE 11. ALUMINUM OVERLOAD AND TOXICITY IN CKD
11.1 To prevent aluminum toxicity, the regular administration of aluminum should be avoided and the dialysate concentration of aluminum should be maintained at <10 µg/L. (EVIDENCE)
   11.1a CKD patients ingesting aluminum should not receive citrate salts simultaneously. (EVIDENCE)
11.2 To assess aluminum exposure and the risk of aluminum toxicity, serum aluminum levels should be measured at least yearly and every 3 months in those receiving aluminum-containing medications. (OPINION)
   11.2a Baseline levels of serum aluminum should be <20 µg/L. (OPINION)
11.3 A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (60 to 200 µg/L); clinical signs and symptoms of aluminum toxicity (Table 31), or prior to parathyroid surgery if the patient has had aluminum exposure. (EVIDENCE) (Algorithms 6 and 7)
   11.3a The test is done by infusing 5 mg/kg of DFO during the last hour of the dialysis session with a serum aluminum measured before DFO infusion and 2 days later, before the next dialysis session. (OPINION)
   11.3b The test is considered positive if the increment of serum aluminum is ≥50 µg/L. (OPINION)
   11.3c A DFO test should not be performed if the serum levels of aluminum are >200 µg/L to avoid DFO-induced neurotoxicity. (OPINION)
11.4 The presence of aluminum bone disease can be predicted by a rise in serum aluminum of ≥50 µg/L following DFO challenge combined with plasma levels of intact PTH of <150 pg/mL (16.5 pmol/L). (OPINION) However, the gold standard for the diagnosis of aluminum bone disease is a bone biopsy showing increased aluminum staining of the bone surface (>15% to 25%) using aluminum stain and often adynamic bone or osteomalacia. (EVIDENCE)

GUIDELINE 12. TREATMENT OF ALUMINUM TOXICITY (ALGORITHM 8 AND ALGORITHM 9)
12.1 In all patients with baseline serum aluminum levels >60 µg/L, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 11, Table 31), the source of aluminum should be identified and eliminated. (OPINION)
12.2 In symptomatic patients with serum aluminum levels >60 µg/L but <200 µg/L or a rise of aluminum after DFO >50 µg/L, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9.) (OPINION)
12.3 To avoid DFO-induced neurotoxicity in patients with serum aluminum >200 µg/L, DFO should not be given until intensive dialysis (6 days per week) with high-flux dialysis membrane and a dialysate aluminum level of <5 µg/L and until the pre-dialysis serum aluminum level has been reduced to <200 µg/L. (OPINION)

GUIDELINE 13. TREATMENT OF BONE DISEASE IN CKD
The therapeutic approach to bone disease in CKD is based on its specific type. As such, this Guideline encompasses 3 parts: Guideline 13A deals with high-turnover and mixed bone disease; Guideline 13B with osteomalacia; and Guideline 13C with adynamic bone disease.

GUIDELINE 13A. HYPERPARATHYROID (HIGH-TURNOVER) AND MIXED (HIGH-TURNOVER WITH MINERALIZATION DEFECT) BONE DISEASE
13A.1 In CKD patients (Stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (Stage 3) or >110 pg/mL (12.1 pmol/L) (Stage 4) on more than 2 consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol, (EVIDENCE) or 1 of its analogs [alfacalcidol (EVIDENCE) or doxercalciferol (OPINION)] should be given to prevent or ameliorate bone disease. (See Guideline 8A.)
13A.2 In CKD patients (Stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol (EVIDENCE) or 1 of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (OPINION) should be used to reverse the bone features of PTH overactivity (ie, high-turnover bone disease), and to treat defective mineralization. (See Guideline 8B.)

GUIDELINE 13B. OSTEOMALACIA
13B.1 Osteomalacia due to aluminum toxicity should be prevented in dialysis patients by maintaining aluminum concentration in dialysate fluid at <10 µg/L and avoiding the use of aluminum-containing compounds (including sucralfate). (OPINION)
13B.2 Aluminum overload leading to aluminum bone disease should be treated with deferoxamine (DFO). (See Guidelines 11 and 12.) (OPINION)
13B.3 Osteomalacia due to vitamin D2 or D3 deficiency or phosphate depletion, though uncommon, should be treated with vitamin D2 or D3 supplementation (see Guideline 7) and/or phosphate administration, respectively. (OPINION)
13B.3a If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (Stage 5), treatment with an active vitamin D sterol may be given. (OPINION) (See Guideline 8B.)
13B.3b Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved. (OPINION)

GUIDELINE 13C. ADYNAMIC BONE DISEASE
13C.1 Adynamic bone disease in stage 5 CKD (as determined either by bone biopsy or intact PTH <100 pg/ml [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)
13C.1a This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy. (OPINION)

GUIDELINE 14. PARATHYROIDECTOMY IN PATIENTS WITH CKD
14.1 Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL [88.0 pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)
14.2 Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy, or total parathyroidectomy with parathyroid tissue autotransplantation. (EVIDENCE)
14.3 In patients who undergo parathyroidectomy the following should be done:
14.3a The blood level of ionized calcium should be measured every 4 to 6 hours for the first 48 to 72 hours after surgery, and then twice daily until stable. (OPINION)
14.3b If the blood levels of ionized or corrected total calcium fall below normal (<3.6 mg/dL [0.9 mmol/L] corresponding to corrected total calcium of 7.2 mg/dL [1.80 mmol/L]), a calcium gluconate infusion should be initiated at a rate of 1 to 2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (4.6 to 5.4...
mg/dL [1.15 to 1.36 mmol/L]). (OPINION) A 10-mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium.

14.3c The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. (OPINION)

14.3d When oral intake is possible, the patient should receive calcium carbonate 1 to 2 g 3 times a day, as well as calcitriol of up to 2 µg/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. (OPINION)

14.3e If the patient was receiving phosphate binders prior to surgery, this therapy may need to be discontinued or reduced as dictated by the levels of serum phosphorus. (OPINION)

14.4 Imaging of parathyroid glands with 99Tc-Sestamibi scan, ultrasound, CT scan, or MRI should be done prior to re-exploration parathyroid surgery. (OPINION)

GUIDELINE 15. METABOLIC ACIDOSIS

15.1 In CKD Stages 3, 4 and 5, the serum level of total CO2 should be measured.

15.1a The frequency of these measurements should be based on the stage of CKD as shown in Table 32. (OPINION)

15.2 In these patients, serum levels of total CO2 should be maintained at ≥22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)

GUIDELINE 16. BONE DISEASE IN THE KIDNEY TRANSPLANT RECIPIENT

16.1 Serum levels of calcium, phosphorus, total CO2 and plasma intact PTH should be monitored following kidney transplantation. (OPINION)

16.1a The frequency of these measurements should be based on the time following transplantation, as shown in Table 33. (OPINION)

16.2 During the first week after kidney transplantation, serum levels of phosphorus should be measured daily. Kidney transplant recipients who develop persistently low levels of serum phosphate (<2.5 mg/dL [0.81 mmol/L]) should be treated with phosphate supplementation. (OPINION)

16.3 To minimize bone mass loss and osteonecrosis, the immunosuppressive regimen should be adjusted to the lowest effective dose of glucocorticoids. (EVIDENCE)

16.4 Kidney transplant recipients should have bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) to assess the presence or development of osteoporosis. (OPINION)

16.4a DEXA scans should be obtained at time of transplant, 1 year, and 2 years post-transplant. (OPINION)

16.4b If BMD t-score is equal to or less than -2 at the time of the transplant or at subsequent evaluations, therapy with parenteral amino-bisphosphonates should be considered. (OPINION)

16.5 Treatment of disturbances in bone and mineral metabolism is determined by the level of kidney function in the transplant recipient as provided in Guidelines 1 through 15 for CKD patients. (OPINION)
GUIDELINES FOR ANEMIA OF CKD

Major Studies

• CHOIR
  o Open label, randomized-control trial of 1432 nondialysis, CKD patients. Two arms of epoetin (Procrit) dose to target hemoglobin levels of 13.5 g/dL (n=715) or to target hemoglobin of 11.3 g/dL (n=717). At baseline, mean hemoglobin level of 10.1 g/dL and a mean GFR of 27 mL/min. About 50% were diabetic. The primary end point was a composite of death, myocardial infarction (MI), hospitalization for congestive heart failure (other than for renal-replacement therapy), and stroke.
  o Early termination due to outcomes (mean duration 16 months). A total of 222 composite events occurred: 125 events in the high-hemoglobin group, as compared with 97 events in the low-hemoglobin group (hazard ratio, 1.34; 95% confidence interval, 1.03 to 1.74; P=0.03). There were 65 deaths (29.3%), 101 hospitalizations for congestive heart failure (45.5%), 25 myocardial infarctions (11.3%), and 23 strokes (10.4%). Seven patients (3.2%) were hospitalized for congestive heart failure and myocardial infarction combined, and one patient (0.5%) died after having a stroke. Patients in the high-hemoglobin group did not reach the 13.5-g/dL target but achieved a mean hemoglobin level of 12.6 g/dL and did not show any quality-of-life benefits.
  o Improvements in the quality of life were similar in the two groups. More patients in the high-hemoglobin group had at least one serious adverse event.
  o CONCLUSIONS: The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with increased risk and no incremental improvement in the quality of life.

• CREATE
  o Open label, randomized trial of 603 patients in 22 countries with stage 3 to 4 CKD (eGFR 15-35 mL/min/1.73 m2) and mild to moderate anemia (hemoglobin 11-12.5 g/dL) using epoetin beta (NeoRecormon, F Hoffman-LaRoche) to two hemoglobin target groups: (1) normal 13 to 15 g/dL or (2) sub-normal 10.5 to 11.5 g/dL. Primary outcome was a composite of 8 cardiovascular events. Secondary end points included left ventricular mass index, quality-of-life scores, and the progression of chronic kidney disease.
  o Subcutaneous erythropoietin (epoetin beta) was initiated at randomization (group 1) or only after the hemoglobin level fell below 10.5 g per deciliter (group 2).
  o 3-year follow-up, no significant difference in cardiovascular-event rates or in all-cause mortality between the 2 treatment groups, but patients in the high-hemoglobin group achieved significantly better quality-of-life outcomes.
    ▪ Complete correction of anemia did not affect the likelihood of a first cardiovascular event (58 events in group 1 vs. 47 events in group 2; hazard ratio, 0.78; 95% confidence interval, 0.53 to 1.14; P=0.20). Left ventricular mass index remained stable in both groups. The mean estimated GFR was 24.9 ml per minute in group 1 and 24.2 ml per minute in group 2 at baseline and decreased by 3.6 and 3.1 ml per minute per year, respectively (P=0.40). Dialysis was required in more patients in group 1 than in group 2 (127 vs. 111, P=0.03).
    General health and physical function improved significantly (P=0.003 and P<0.001, respectively, in group 1, as compared with group 2). There was no significant difference in the combined incidence of adverse events between the two groups, but hypertensive episodes and headaches were more prevalent in group 1.
  o CONCLUSIONS: In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events.

• TREAT
  o METHODS: In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a
hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g per deciliter. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.

- **RESULTS:** Death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% confidence interval [CI], 0.94 to 1.17; P=0.41). Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo (hazard ratio, 1.06; 95% CI, 0.95 to 1.19; P=0.29). Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo (hazard ratio, 1.92; 95% CI, 1.38 to 2.68; P<0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 patients assigned to placebo (P<0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

- **CONCLUSIONS:** The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits.

**Aranesp to Epoetin Conversion**

<table>
<thead>
<tr>
<th>Darbepoetin (Aranesp) Once Weekly Dose</th>
<th>Nephrology Weekly Dose Ranges for Epoetin (Epogen, Procrit)</th>
<th>Non-Nephrology Typical Once Weekly Doses Epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.25 mcg</td>
<td>&lt; 2,500 units</td>
<td></td>
</tr>
<tr>
<td>12.5 mcg</td>
<td>2,500 – 4,999 units</td>
<td></td>
</tr>
<tr>
<td>25 mcg</td>
<td>5,000 – 10,999 units</td>
<td>10,000 units</td>
</tr>
<tr>
<td>40 mcg</td>
<td>11,000 – 17,999 units</td>
<td></td>
</tr>
<tr>
<td>60 mcg</td>
<td>18,000 – 33,999 units</td>
<td>20,000 units</td>
</tr>
<tr>
<td>100 mcg</td>
<td>34,000 – 59,999 units</td>
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<tr>
<td>150 mcg</td>
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<td>&gt; 60,000 units</td>
</tr>
<tr>
<td>200 mcg</td>
<td>≥ 90,000 units</td>
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</tr>
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</table>
GUIDELINES FOR CARDIORENAL SYNDROME

Stage A Therapy

Recommended Therapies to Reduce Risk Include:
- Treating known risk factors (hypertension, diabetes, etc.)
- Drug therapy consistent with contemporary guidelines
- Avoiding behaviors increasing risk (i.e., smoking, excessive consumption of alcohol, illicit drug use)
- Periodic evaluation for signs and symptoms of HF
- Ventricular rate control or sinus rhythm restoration
- Noninvasive evaluation of LV function
- Drug Therapy –
  - Angiotensin Converting Enzyme Inhibitors (ACEI)
  - Angiotensin Receptor Blockers (ARBs)

Stage B Therapy

Recommended Therapies:
- General Measures as advised for Stage A
- Drug therapy for all patients
  - ACEI or ARBs in appropriate patients (see text)
- Beta-blockers
- ICDs in appropriate patients
- Coronary revascularization in appropriate patients
- Valve replacement or repair in appropriate patients

Stage C Therapy

(Reduced LVEF with Symptoms)

Recommended Therapies:
- General measures as advised for Stages A and B
- Diuretics for fluid retention
- ACEI
- Beta-blockers
- Drug therapy for selected patients
- Aldosterone Antagonists
- ARBs
- Digitalis
- Hydralazine/nitrates
- ICDs in appropriate patients
- Cardiac resynchronization in appropriate patients
- Exercise Testing and Training

Stage D Therapy

Recommended Therapies Include:
- Control of fluid retention
- Referral to a HF program for appropriate pts
- Discussion of options for end-of-life care
- Informing re: option to inactivate defibrillator
- Device use in appropriate patients
- Surgical therapy
  - Cardiac transplantation
  - Mitral valve repair or replacement
  - Other
- Drug Therapy –
  - Positive inotropic infusion as palliation in appropriate patients
# Diablo Nephrology Nurse Practitioner Protocol

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## Cardiovascular Medications Useful for Treatment of Various Stages of Heart Failure

### Slide 1 of 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Captopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Enalapril</td>
<td>H, DN</td>
<td>Asymptomatic LVSD</td>
<td>HF</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Moexipril</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perindopril</td>
<td>H, CV Risk</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quinapril</td>
<td>H</td>
<td>-</td>
<td>HF</td>
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<tr>
<td>Ramipril</td>
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<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
</tbody>
</table>

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

### Slide 2 of 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>H, DN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Losartan</td>
<td>H, DN</td>
<td>CV Risk</td>
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<td>H</td>
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<td>-</td>
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<tr>
<td>Telmisartan</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valsartan</td>
<td>H, DN</td>
<td>Post MI</td>
<td>Post MI, HF</td>
</tr>
</tbody>
</table>

### Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>H</td>
<td>-</td>
<td>HF</td>
</tr>
</tbody>
</table>

CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Asymptomatic LVSD, Asymptomatic left ventricular systolic dysfunction; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.
1. Start with a loop diuretic. If giving BID+, beware of nocturia (ie, Lasix = last six hrs).
2. If symptomatic edema or DOE/orthopnea persists, add thiazide 30 minutes before loop.
3. Add aldosterone antagonists, if still symptomatic.
   a. Spironolactone as 1st choice (RALES showed benefit for NYHA class III/IV).
   b. EMPHASIS-HF shows eplerenone with benefits for NYHA class II.
**Sodium restriction:** New IOM recommendation for 1.5 daily.
- 1 teaspoon of salt = 2300 mg of sodium.

**Fluid restriction:** 1.2 – 1.5 L daily.
**OTHER GUIDELINES: HYPERKALEMIA, TRANSPLANT, & HYPERTENSION**

**Hyperkalemia**
Commonly seen in later CKD stages or with type IV renal tubular acidosis.  
Renal diet = 2 g of potassium daily.  
Look for medications that can cause hyperkalemia:
- ACE inhibitors.
- ARBs.
- Potassium-sparing diuretics: spironolactone, eplerenone, trimaterene, amiloride.
- Beta-blockers.
- Digoxin.
- Antibiotics: Bactrim/Septra, pentamidine.
- Immunosuppressive medications: tacrolimus, cyclosporine.
- Heparin.
- Supplements:
  - Potassium
  - Alfalfa
  - Amino Acids (Aminocaproic acid, Arginine, Lysine)
  - Dandelion
  - Dried toad skin
  - Hawthorne Berry
  - Horsetail
  - Lilly of the Valley
  - Milkweed
  - Nettle
  - Noni Juice
  - Siberian Ginseng

**Renal Transplant**

<table>
<thead>
<tr>
<th>Drug</th>
<th>6 months</th>
<th>Maintenance</th>
<th>CAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>8 – 12</td>
<td>5 – 7</td>
<td>3 – 5</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>150 – 200</td>
<td>80 – 130</td>
<td>50 – 70</td>
</tr>
<tr>
<td>Rapamune w/ MMF</td>
<td>8 – 12</td>
<td>5 – 7</td>
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</tr>
<tr>
<td>Rapamune w/o MMF</td>
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<td>10</td>
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</tr>
</tbody>
</table>

**Health Maintenance**
Monitor fasting lipid panel.  
Annual dermatologic exams.
**Diablo Nephrology Nurse Practitioner Protocol**


### Evaluation

**Classification of Blood Pressure (BP)**

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension, Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension, Stage 2</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

*See Blood Pressure Measurement Techniques (reverse side)

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure

**Diagnostic Evaluation of Hypertension**
- Assess risk factors and co-morbidities.
- Reveal identifiable causes of hypertension.
- Assess presence of target organ damage.
- Conduct history and physical examination.
- Obtain laboratory tests: urinalysis, blood glucose, hemoglobin and lipid panel, serum creatinine, uric acid, and calciums. Optional: urinalysis/creatinine ratio.
- Obtain electrocardiogram.

**Assess for Major Cardiovascular Disease (CVD) Risk Factors**
- Hypertension
- Obesity
- Diabetes mellitus
- Smoking

**Assess for Identifiable Causes of Hypertension**
- Sleep apnea
- Drug-induced
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease

**Blood Pressure Measurement Techniques**

<table>
<thead>
<tr>
<th>Method</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>Two readings, 5 minutes apart, sitting in chair.</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Sphygmomanometer (brachial) or automated device.</td>
</tr>
<tr>
<td>Patient self-check</td>
<td>Provides information on response to therapy.</td>
</tr>
</tbody>
</table>

**Principles of Lifestyle Modification**

- Limit alcohol intake to 2 drinks/day for men and 1 drink/day for women.
- Dietary salt intake of less than 1500 milligrams per day.
- Regular aerobic physical activity, at least 30 minutes per day, 5 days per week.
- Weight reduction: moderate weight loss (5-10% body weight).

**Compliance Indications and Individual Risk Classes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Therapy Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>THZ, BB, ACEI, ARB, ALDO ANT</td>
</tr>
<tr>
<td>Post myocardiual infarction</td>
<td>BB, ACEI, ALDO ANT</td>
</tr>
<tr>
<td>High CVD risk</td>
<td>THZ, BB, ACEI, BB, BB, ACEI, AR, ARB</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACEI AR, ALDO ANT</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>THZ, ACEI</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>ACEI AR, ALDO ANT</td>
</tr>
</tbody>
</table>

**Strategies for Improving Adherence to Therapy**

- Foster physician-patient relationships.
- Involve patients in decision-making regarding therapy.
- Physician should consider their patients' cultural beliefs and individual attitudes in formulating therapy.

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The National High Blood Pressure Education Program is coordinated by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Copies of the JNC 7 Report are available on the NHLBI Web site at: http://www.nhlbi.nih.gov or from the NHLBI: Health Information Center, P.O. Box 3010, Bethesda, MD 20824-3010. Phone: 301-592-8573 or 202-625-1285. Fax: 301-592-8063.

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