A Quick Guide to Evidence-Based Chronic Kidney Disease Care for the Primary Care Physician

Chester H. Fox, MD[1]
Vasu Voleti, MBBS[1]
Linda S. Khan, PhD[1]
Brian Murray, MD[1]
Joseph Vassalotti, MD[2,3]

[1]University at Buffalo, Buffalo, NY; [2]National Kidney Foundation, New York, NY; [3]Mount Sinai School of Medicine, New York, NY

Abstract: With the aging of the US population and the increase in hypertension, diabetes mellitus, and obesity, the prevalence of chronic kidney disease (CKD) is increasing in the United States. Its prevalence rate has risen to 13.1% of the US population. Patients with CKD experience poor outcomes and have high health care costs. Chronic kidney disease is also a major cardiovascular disease risk factor. In fact, most people with CKD die of heart disease before they progress to end-stage renal disease. The National Kidney Foundation has produced evidence-based guidelines known as the Kidney Disease Outcomes Quality Initiative (KDOQI). These guidelines outline many things that the primary care physician can do to delay the progression of CKD, and to arrange for early referral for the prevention of future complications. However, there is limited knowledge and uptake of these guidelines because of their length and and complexity. Patients with CKD risk factors, hypertension, diabetes mellitus, cardiovascular disease, a family history of CKD, and those older than 60 years should be screened using 2 tests: 1) the estimated glomerular filtration rate and 2) the urinary albumin-creatinine ratio. These tests allow the diagnosis and stratification of CKD into 5 stages. This article synthesizes the key evidence-based behaviors and clinical action plan that primary care physicians can implement to treat CKD and its complications.

Keywords: chronic kidney disease; kidney failure; renal insufficiency; evidence-based care; chronic disease management

Prevalence

Chronic kidney disease (CKD) is increasing in prevalence in the United States. According to the National Health and Nutrition Examination Survey (NHANES), data from 1988 to 1994 demonstrated that CKD was present in 10% of the US population. This same survey completed during the period of 1999 to 2004 revealed an increase in this prevalence to 13.1%. The increase in hypertension and diabetes mellitus has also contributed the increasing CKD prevalence.[1]

The common risk factors for CKD are diabetes mellitus, hypertension, cardiovascular disease (CVD), a family history of CKD, and age older than 60 years.[2] Less common risk factors include autoimmune diseases, infections, kidney stones, cancer, and nephrotoxic drug exposure. Minority populations are much more likely to develop CKD.[3,4] Compared with the white population, CKD is 2 times as prevalent in Hispanics and 4 times as prevalent in blacks.[5,6]

CKD is a CVD Equivalent

The likelihood of having a myocardial infarction (MI) is the same for a patient whether they have CKD, diabetes mellitus, or a previous MI.[7] The risk of death, cardiovascular

Correspondence: Chester H. Fox, MD
1315 Jefferson Ave., Buffalo,
New York, NY 14208.
Tel: 716-332-3797
Fax: 716-898-4750
E-mail: chetfox@gmail.com

events, and hospitalization increases in a graded fashion as the estimated glomerular filtration rate (eGFR) decreases below 60 mL/min/1.73m.[2,8] Also, after a MI, the risk of death, reinfarction, congestive heart failure, stroke, or cardiac arrest increases with declining kidney function.[9] In one study, when the eGFR decreased below 45 mL/min/1.73m^2, mortality from cardiovascular disease was noted to increase more than 3-fold.[10]

Limited Implementation of Evidence-Based Guidelines

The National Kidney Foundation published evidence-based guidelines called the Kidney Disease Outcomes Quality Initiative (KDOQI). However, there is limited knowledge and use of these guidelines by primary care physicians.[11,12] We speculate that complexity and time constraints are the primary barriers to implementation since these guidelines are complex and lengthy.[3,13–15] Primary care physicians have competing time demands,[16] and a typical office visit of approximately 15 minutes does not allow for either preventive screening or chronic disease management to be performed completely. Two studies completed by the Duke School of Public Health revealed implementation of the entire grade A and grade B evidence from the US Preventive Services Task Force would take 7.4 hours per day, and implementing chronic disease management would take an additional 3.5 hours per day.[17,18] Streamlined guidelines are needed to meet recommended standards for quality care.[17,18]

Making the Diagnosis

A patient is diagnosed CKD when either the urinary albumin-creatinine ratio (ACR) is $>$ 30 mg/g or when the eGFR, as measured by the Modification of Diet in Renal Diseases (MDRD) Study equation is $<$ 60 mL/min/1.73m^2 on at least 2 different occasions over 3 or more months.[2,19] These 2 simple tests facilitate diagnosis of CKD by all clinicians, irrespective of the etiology.

Stage 1 and 2 CKD can be classified as persistent ACR $>$ 30 mg/g and eGFR $\geq$ 60 mL/min/1.73m^2. Stage 3 CKD occurs when the patient's eGFR is $>$ 30 mL/min/1.73m^2 but $<$ 60 mL/min /1.73m^2. Stage 4 CKD occurs when their eGFR is $<$ 30 mL/min /1.73m^2. Primary care physicians will primarily be treating patients with stage 1 to 3 CKD. Referral to a nephrologist is recommended once the patient reaches stage 4. Referral to a nephrologist should be considered in patients with an eGFR $>$ 30 mL/min/1.73m^2, resistant hypertension, $>$ 30% loss of eGFR over 4 months, hyperkalemia $>$ 5.5mEq/L, when the CKD diagnosis is unclear, or the clinical action plan cannot be implemented. Early referral to a nephrologist has been shown to improve outcomes.[3,20] All patients at risk for CKD should also have a urinalysis with microscopy. If there is hematuria, white blood cell casts, or red blood cell casts, then the patient should have a rapid referral to a nephrologist or be further evaluated. If there are any abnormalities in the work-up (Table 1), early referral is indicated for evaluation of possible reversible causes of CKD. These patients may require an early renal biopsy to prevent end-stage renal disease.[3]

Preventing CKD Progression

A CKD clinical action plan should focus on risk factor reduction for blood pressure and glycemic control in patients with diabetes mellitus to prevent cardiovascular disease and delay or slow loss of kidney function. Additional interventions are detection and treatment of CKD complications, discontinuing nephrotoxic medications, and early referral to a nephrologist. The main complications of CKD are hypertension, diabetes mellitus, CVD, anemia, and bone mineral metabolism disorders.[21–26]

Managing the Complications of CKD

CVD Risk Factors

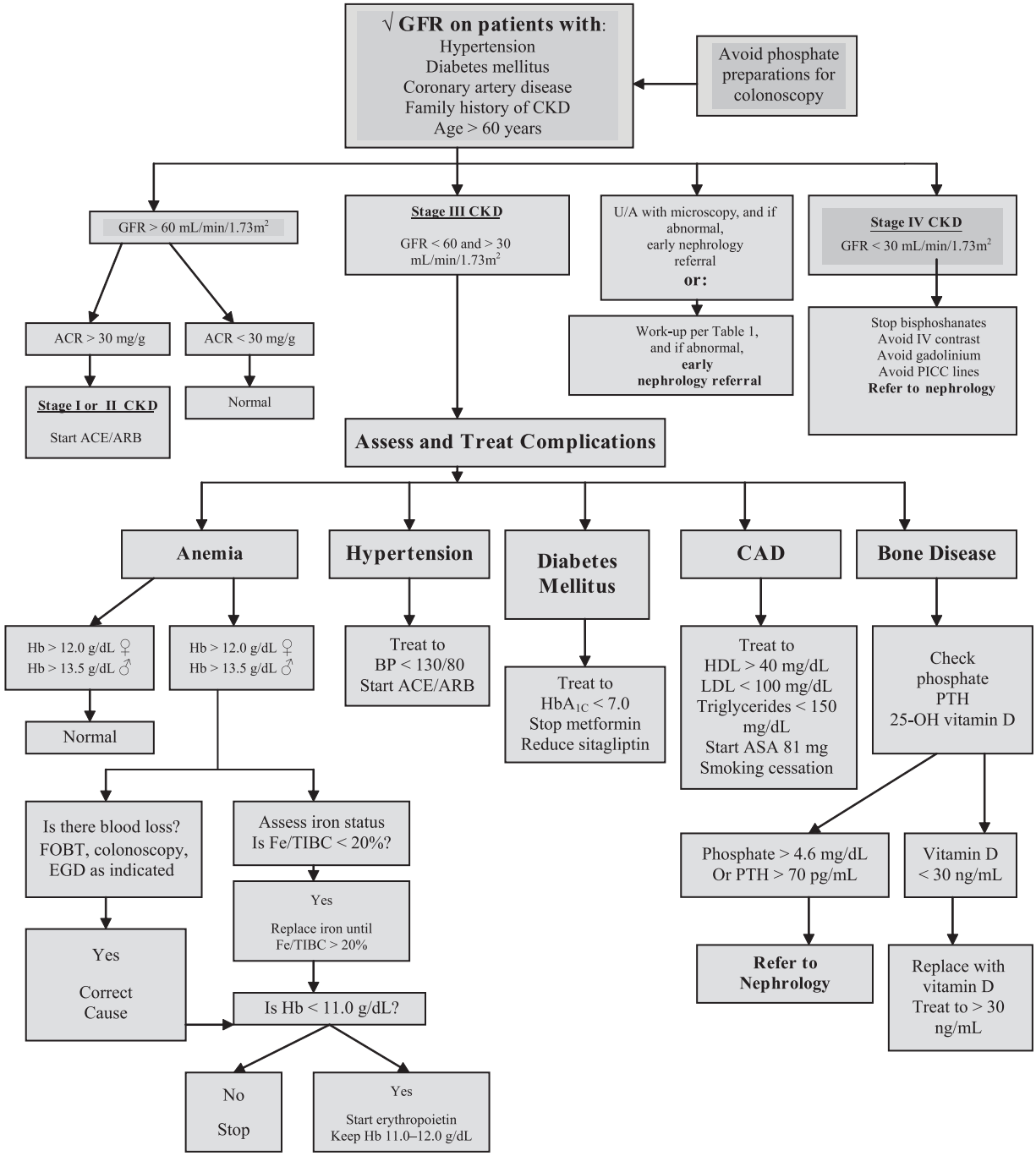
The main modifiable CVD risk factors in patients CKD are hypertension, diabetes mellitus, hyperlipidemia, and smoking. The goal for hypertension control is to maintain blood pressure $<$ 130/80 mm Hg.[27] Whenever possible, all patients should be on an angiotensin converting enzyme inhibitor (ACE) or an angiotensin receptor blocker (ARB). Angiotensin receptor blockers are very similar to ACEs, but

Table 1. Work-up for Nondiabetic CKD or Abnormal Urinalysis

- CBC, electrolytes, uric acid
- Calcium, phosphorous
- 24-hour urine protein
- ANA, ANCA
- C3, C4, CH50
- Anti-GBM antibody
- HBsAg, Hep C Ab, HIV
- Serum protein electophoresis
- Renal ultrasound and flow dopplers

Abbreviations: CBC, complete blood count; ANA, antinuclear antibodies; ANCA, antinuclear cytoplasmic antibody, C3, C4, CH50-complement studies; GBM, glomerular basement membrane; HBsAG, hepatitis B surface antigen; Hep C Ab, hepatitis C virus antibodies; HIV, human immunodeficiency virus.

Figure 1. Chronic Kidney Disease Management – Primary Care



Abbreviations: GFR, glomerular filtration rate; ACR, albumin/creatinine ratio; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; U/A, urinalysis; PICC, peripherally inserted central catheter; Hb, hemoglobin; PTH, parathyroid hormone; FOBT, fecal occult blood testing; EGD, esophagogastroduodenoscopy; Fe/TIBC, iron/total iron binding capacity.

they cause less cough and have a lower tendency toward development of hyperkalemia.[28] The GFR should be checked 2 weeks after initiation of therapy. If it has declined < 25%, then the ACE or ARB can be continued. If it declines > 25%, then it should be discontinued and a work-up for renal artery stenosis should be performed. If this shows stenosis, then the patient should be referred to a nephrologist. Other medicines that may be considered for treating hypertension in CKD are diuretics, beta-blockers, and nondihydropyridine calcium channel blockers. Centrally acting agents, such as clonidine, are also appropriate. If more than 3 drugs are required, or blood pressure is difficult to control, referral to a nephrologist is indicated.[13] Unless there are contraindications, patients with CKD should be considered as candidates for aspirin 81 mg daily for prevention of CVD.

The goal of diabetes management is to keep the hemoglobin A1C (Hb_{A1C}) < 7.0%. Metformin generally should not be used in stage 3 to 5 CKD, and the dose of sitagliptin needs to be reduced. All other diabetes regimens can be utilized.[29] The goals for hyperlipidemia management are: having an HDL > 40 mg/dL, an LDL < 100 mg/dL, and a triglyceride level < 150 mg/dL. Although current guidelines continue to recommend an LDL of < 100 mg/dL, since CKD is a coronary artery disease (CAD) equivalent, this may soon change to an LDL of < 70 mg/dL.[14,30] High-dose statins have recently been shown to improve outcomes in patients with CKD.[31]

Smoking is a known cardiovascular risk factor and is also associated with CKD progression.[32,33] Advice on smoking cessation is always warranted in patients with CKD. The American Cancer Society has smoking quit lines in all states, which is a helpful resource for physicians to communicate to their patients.

Diagnosing and Treating Anemia

Anemia is defined as having a hemoglobin of < 13.5 g/dL in men or < 12.0 g/dL in women. If this is present, blood loss must first be ruled out. This may require a colonoscopy and/or an esophagogastroduodenoscopy (EGD). The next thing that must be ruled out is iron-deficiency anemia. Evaluation should include complete blood count, ferritin, absolute reticulocyte count, and transferrin saturation (Fe/TIBC). If it is < 20%, then iron should be supplemented. Oral iron is often ineffective for this and intravenous (IV) iron is often necessary. If it is > 20% and the hemoglobin is < 11.0 g/dL, erythropoietin-stimulating proteins can be administered.[34] This can be accomplished by using erythropoietin (EPO) or darbepoietin (DPO), which can be self-administered. Hemoglobin levels should be checked at least monthly, and Fe/TIBC levels can be checked quarterly. The target is to keep the hemoglobin between 11.0 and 12.0 g/dL, and the Fe/TIBC > 20%. The Food and Drug Administration (FDA) label for EPO and DPO uses a target between 10 and 12 g/dL.

Bone Mineral Metabolism Disorders

As the kidney starts to fail, less calcium is reabsorbed. As serum calcium starts to decrease, a signal is sent to the parathyroid gland, which releases parathyroid hormone (PTH). This causes resorption of the bone and the release of both calcium and phosphate into the bloodstream. The net result of these processes is secondary hyperparathyroidism and hyperphosphatemia. In addition, many patients with CKD are also vitamin D deficient. This causes an inability to absorb calcium, and is another mechanism for producing secondary hyperparathyroidism. Correction of vitamin D deficiency suppresses PTH and prevents vascular disease.[26,35] If a patient's vitamin D level is < 30 pg/mL, then this should be replaced with 25 0H vitamin D. This can be accomplished by giving 50 000 units monthly. The vitamin D level can be rechecked at 3 months. If the level is still < 30 pg/mL, then the 50 000 units can be administered weekly for 2 months, or until the level is > 30 pg/mL. If the patient has significant hyperparathyroidism, as defined by a PTH > 70 pg/mL, or hyperphosphatemia with a serum phosphate > 4.5 mg/dL, then the patient should be referred to a nephrologist.[36]

Avoiding Nephrotoxic and Contraindicated Medications

There are several medications that should be avoided in patients with CKD:

1. Phosphate preparations for colonoscopy, such as Fleet® Phospho soda®, can cause a specific type of acute CKD even in patients without previous CKD, called acute phosphate nephropathy.[37]
2. Nonsteroidal anti-inflammatory drugs (NSAIDS) and cox-2 inhibitors can reduce kidney function and make hypertension control more difficult.[38]
3. Metformin, although not directly toxic to the kidney, can have the rare but fatal side effect of lactic acidosis in patients with CKD. It is therefore recommended that it be discontinued if the patient's GFR is < 60 mL/min/1.73m^2, although the FDA package insert recommends avoidance when the

serum creatinine is > 1.5 mg/dL in men and > 1.3 mg/dL in women.[29]

4. Bisphosphanates should be avoided with patients with an eGFR < 30 mL/min/1.73m^2 as per the FDA package insert.
5. Iodinated contrast used in CT scans and angiography can cause contrast-induced nephropathy.[39]
6. Gadolinium can cause a nephrogenic systemic fibrosis in patients with an eGFR < 30 mL/min/1.73m^2.[40,41]
7. ACEs, ARBs, and thiazide diuretics should be avoided in advanced stages of CKD. Nephrology care and advice is important with all of these patients.

Preserving Vascular Access

Preserving vascular access in patients with CKD is critically important for the prevention of future complications. Many of these patients will eventually require dialysis. If the veins in the nondominant arm can be preserved, and there is early enough referral to a nephrologist, then an elective fistula can be placed prior to the start of hemodialysis. If the fistula is not in place by the time the patient requires hemodialysis, then a central venous catheter must be placed in the neck, with the attendant risks of infection. The saying "fistulas first and catheters last" summarizes this recommendation.[42,43] The 3 things that the primary care physician can do to improve vascular access are: 1) tell the patient to have all blood drawn from their dominant arm; 2) avoid the use of peripherally inserted central catheters (PICC lines), using the alternative single lumen central catheter instead; and 3) refer the patient to a nephrologist when the GFR falls below 30 mL/min /1.73m^2 if not sooner.

Summary

Chronic kidney disease is a growing US public health problem. Increased awareness and implementation of the KDOQI evidence-based guidelines for CKD by primary care physicians could delay the progression disease, reduce mortality, and improve the quality of life for patients.

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References

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038–2047.
2. Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am J Kidney Dis*. 2007;50(2):169–180.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1–S266.
4. Buckalew VM Jr. End-stage renal disease: can dietary protein restriction prevent it? *South Med J*. 1994;87(10):1034–1037.
5. Agodoa L. Minorities and ESRD. Review: African American study of kidney disease and hypertension clinical trial. *Nephrol News Issues*. 1995;9(11):18–19.
6. Agodoa L. African American Study of Kidney Disease and hypertension (AASK)—clinical trial update. *Ethn Dis*. 1998;8(2):249–253.
7. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to know? Where do we go from here? Special report from the National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis*. 1998;32(5 suppl 3):S1–S199.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296–1305.
9. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351(13):1285–1295.
10. Hallan SI, Dahl K, Oien CM, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ*. 2006;333(7577):1047.
11. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NR. Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis*. 2006;48(2):192–204.
12. Fox CH, Brooks A, Zayas LE, McClellan W, Murray B. Primary care physicians' knowledge and practice patterns in the treatment of chronic kidney disease: an Upstate New York Practice-based Research Network (UNYNET) study. *J Am Board Fam Med*. 2006;19(1):54–61.
13. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5 suppl 1):S1–S290.
14. Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis*. 2003;41(4 suppl 3):I–IV, S1–S91.
15. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. *Am J Kidney Dis*. 2001;37(1 suppl 1):S182–S238.
16. Jaen CR, Stange KC, Nutting PA. Competing demands of primary care: a model for the delivery of clinical preventive services. *J Fam Pract*. 1994;38(2):166–171.
17. Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? *Am J Public Health*. 2003; 93(4):635–641.
18. Ostbye T, Yarnall KS, Krause KM, et al. Is there time for management of patients with chronic diseases in primary care? *Ann Fam Med*. 2005;3(3):209–214.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461–470.
20. Barrett BJ. Managing progressive renal disease before dialysis. *Can Fam Physician*. 1999;45:977–984.
21. Johnson DW. Evidence-based guide to slowing the progression of early renal insufficiency. *Intern Med J*. 2004;34(1–2):50–57.

22. Boos C. Cardiovascular protection with ace inhibitors - more HOPE for EUROPA? *Med Sci Monit*. 2004;10(12):SR23–SR28.
23. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int*. 2004;66(2):753–760.
24. Silverberg D. Outcomes of anaemia management in renal insufficiency and cardiac disease. *Nephrol Dial Transplant*. 2003;(18 suppl 2):ii7–ii12.
25. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51(15):1448–1454.
26. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281.
27. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289(19):2560–2572.
28. Abbott KC, Bakris GL. What have we learned from the current trials? *Med Clin North Am*. 2004;88(1):189–207.
29. KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*. 2007;49(2 suppl 2):S12–S154.
30. Molitch ME. Management of dyslipidemias in patients with diabetes and chronic kidney disease. *Clin J Am Soc Nephrol*. 2006;1(5):1090–1099.
31. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51(15):1448–1454.
32. McCullough PA. Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. *Curr Opin Nephrol Hypertens*. 2004; 13(6):591–600.
33. Wu-Wong JR, Nakane M, Traylor L, Ruan X, Kroeger PE, Tian J. Cardiovascular disease in chronic kidney failure: is there a role for vitamin D analogs? *Curr Opin Investig Drugs*. 2005;6(3):245–254.
34. KDOQI; National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis*. 2006;47(5 suppl 3):S11–S145.
35. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117(4):503–511.
36. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis*. 2007;50(3):471–530.
37. Markowitz GS, Radhakrishnan J, D'Agati VD. Towards the incidence of acute phosphate nephropathy. *J Am Soc Nephrol*. 2007; 18(12):3020–3022.
38. Analgesic-associated kidney disease. Natl Inst . *Natl Inst Health Consens Dev Conf Consens Statement*. 1984;5(2):6.
39. Davidson C, Stacul F, McCullough PA, et al. Contrast medium use. *Am J Cardiol*. 2006;98(6A):42K–58K.
40. Perazella MA, Reilly RF. Nephrogenic systemic fibrosis: recommendations for gadolinium-based contrast use in patients with kidney disease. *Semin Dial*. 2008;21(2):171–173.
41. Stratta P, Canavese C, Aime S. Gadolinium-enhanced magnetic resonance imaging, renal failure and nephrogenic systemic fibrosis/ nephrogenic fibrosing dermopathy. *Curr Med Chem*. 2008;15(12):1229–1235.
42. Lenz O, Sadhu S, Fornoni A, Asif A. Overutilization of central venous catheters in incident hemodialysis patients: reasons and potential resolution strategies. *Semin Dial*. 2006;19(6):543–550.
43. Owen WF Jr. Patterns of care for patients with chronic kidney disease in the United States: dying for improvement. *J Am Soc Nephrol*. 2003; 14(7 suppl 2):S76–S80.