National Kidney Foundation®

KDOQI
Kidney Disease Outcomes Quality Initiative

KDOQI Clinical Practice Guidelines and Commentaries

Research Recommendations

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Guideline 1: Timing of Hemodialysis Initiation

Research Recommendations

- Better predictive instruments for determining when, if ever, an individual is likely to require KRT are important for optimizing patient preparation, including timely creation of vascular access, PD catheter placement, and pre-emptive transplantation, while minimizing unnecessary procedures, such as vascular access surgeries and donor and recipient transplantation evaluations.
- Research regarding how to conduct patient education and to facilitate the decision-making process when challenged with the need for KRT has the potential to enhance individualized patient care.

Guideline 2: Frequent and Long Duration Hemodialysis

- Determine the effect of short frequent hemodialysis on mortality and hospitalizations.
- Determine the mechanisms responsible for arteriovenous access complications in patients undergoing short frequent hemodialysis
- Gather more robust data regarding the optimal type of vascular access for short frequent hemodialysis
- Determine the mechanisms responsible for hypotension during short frequent hemodialysis in order to develop appropriate treatments and/or prevention measures.
- Determine the implications of intradialytic hypotension in the context of short frequent hemodialysis on patient quality of life and morbidity.
- Measure the rate of loss of residual kidney function in new patients starting short frequent hemodialysis.
- Identify factors responsible for lack of long-term adherence to short frequent hemodialysis.
- Determine the effect of home long frequent hemodialysis therapies (3 to 6 nights per week) on mortality and hospitalizations.
- Gather more robust data regarding the optimal type of access for frequent hemodialysis and the type of cannulation technique for home hemodialysis patients.
- Determine the clinical implications of accelerated loss of residual kidney function that occurs with long frequent hemodialysis.
- Validate the increased burden on caregivers perceived by patients receiving long frequent hemodialysis by comparison with the actual burden as perceived by caregivers.
- Develop methods to ameliorate caregiver burden associated with long frequent hemodialysis.
- Identify factors governing long-term adherence to long frequent hemodialysis.
- Obtain better estimates of the risk of pregnancy-related complications with conventional HD vs. long frequent HD.

Guideline 3: Measurement of Dialysis: Urea Kinetics

- Future research should be directed to better understand the residual syndrome with focus on treatment and improved survival while not losing sight of small solute removal, which must be considered the most important life sustaining aspect of hemodialysis.

Guideline 4: Volume and Blood Pressure Control: Limits on Treatment Time and Ultrafiltration Rate

- Testing and validation of practical tools to ascertain dry weight
- Randomized controlled trials determining the risk / benefit of altering dialysis sodium
- Randomized trials determining the effect of altering ultrafiltration rate on clinical outcomes
- Assessment of an ideal dietary sodium intake for dialysis patients
- Studies to further our understanding of both a minimum and an ideal treatment time while assessing clinical outcomes and patient preferences

Guideline 5: New Hemodialysis Membranes

- Further understanding into the cost/benefit ratio of high vs low-flux membranes
- Additional research is needed to understand whether there is a clinical benefit associated with hemodiafiltration vs conventional hemodialysis

Guideline 2: Coronary Artery Disease

Research Recommendations

- Prospective trials are needed to examine the accuracy of noninvasive imaging in dialysis patients and its utility for clinical management.

Guideline 3: Acute Coronary Syndromes

Research Recommendations

- Clinical trials of Acute Coronary Syndrome (ACS) treatment are required that specifically target all ranges of Chronic Kidney Disease (CKD), including dialysis patients.

Guideline 4: Chronic Coronary Artery Disease

Research Recommendations

- Randomized trials of percutaneous coronary intervention (PCI) are required, using sirolimus-eluting or paclitaxel-eluting stents compared to coronary bypass surgery.

Guideline 5: Valvular Heart Disease

Research Recommendations

- Observational studies of the newer generation of bioprosthetic valves (e.g., stentless valves) are required.
- Studies on the timing of valve replacement in relation to survival will provide valuable information (e.g., do clinicians wait too long to refer patients for surgery?).

Guideline 6: Cardiomyopathy (Systolic or Diastolic Dysfunction)

Research Recommendations

- More clinical trials on treatment of Congestive Heart Failure (CHF) in dialysis patients are required. A randomized, prospective trial on primary beta-blocker therapy to reduce the risk of CHF and death would be a worthwhile project in dialysis patients, especially in diabetics.
- Valuable information may be derived from a large longitudinal cohort study of echocardiographic changes in the incident chronic hemodialysis (HD) and peritoneal dialysis (PD) populations, in the modern era of cardiac

therapeutics.
- Further large cross-sectional studies are required to examine the prevalence of cardiomyopathy in the chronic HD and PD populations.

Guideline 7: Dysrhythmia

Research Recommendations

- Modifications in the Centers for Medicare and Medicaid Services (CMS) form are required to increase the accuracy of data capture for arrhythmias and near-fatal cardiac arrest in dialysis patients.
- Studies are needed to assess the outcome and the effectiveness of different preventive and treatment strategies to improve the dismal outcome of near-fatal arrhythmias in dialysis patients.
- There is a strong need to evaluate the mechanisms of sudden death in this population.

Guideline 8: External Defibrillation

Research Recommendations

- Observational studies are required to examine mortality trends after the implementation of this guideline.

Guideline 9: Cerebrovascular Disease

Research Recommendations

- Stroke risk is very high in the CKD population. Effective screening strategies do not exist, nor do studies assessing interventions. Studies addressing these issues are greatly needed.

Guideline 10: Peripheral Vascular Disease (PVD)

Research Recommendations

- Further studies are warranted to examine the feasibility and effectiveness of ankle: brachial or toe: brachial indices as screening tests for asymptomatic PVD in reducing limb amputation rates.

Guideline 11: Diabetes

Research Recommendations

- Long-term, randomized controlled trials are needed to strengthen the evidence for the direct application of the American Diabetes Association (ADA) recommendations to patients on dialysis.
- More research is needed on the effect of renal dietary restrictions in diabetic patients.

Guideline 12: Blood Pressure

Research Recommendations

- More studies are necessary to better determine goal blood pressures in dialysis patients.
- Studies are needed to determine which antihypertensive drugs are best suited for dialysis patients.
- More studies are necessary to determine optimal dosing (dose and time of administration) of antihypertensive drugs in dialysis patients.
- Further studies are needed to ascertain the potential advantage of daily dialysis over dialysis performed 3 times weekly to achieve better blood pressure control and better cardiovascular outcomes.

Guideline 14: Smoking, Physical Activity, and Psychological Factors

Research Recommendations

Smoking

- Studies are required in CKD patients to examine the pharmacokinetics/safety of pharmacotherapies known to be effective in smoking cessation.
- Randomized trials are needed to determine the most effective interventions for smoking cessation in dialysis patients.
- Randomized, controlled trials are needed to determine the effects of smoking cessation on cardiovascular and all-cause outcomes in dialysis patients.

Physical activity

- Randomized clinical trials are needed to study the effects of exercise training on cardiovascular risk in dialysis patients.
- Studies are required to determine the optimal exercise prescription and to develop practical ways of incorporating physical activity and assessment of physical functioning into the routine care of dialysis patients.
- Studies are needed to define the barriers to exercise in dialysis patients and to develop motivational strategies to increase participation in regular physical activity.
- Studies are required to determine how to effectively incorporate physical activity into the routine care of dialysis patients.

Psychological factors

- Research is needed to study the presence of psychological distress in dialysis patients.
- Further studies are required to examine the impact of psychological distress on cardiovascular functioning and outcomes in dialysis patients.
- Studies are required in dialysis patients to examine the impact of therapeutic interventions, which are used to treat psychological conditions associated

with cardiovascular disease (CVD), on psychological states and cardiovascular events.

Guideline 15: Anemia

Research Recommendations

- Studies are needed to determine the most appropriate hemoglobin value to reduce the risk of nonatherosclerotic heart disease.

Guideline 16: Arterial Stiffness, Vascular and Valvular Calcification, Calcium, Phosphorus and PTH

Research Recommendations

- Further studies are required to examine the use of statins in patients with pulse pressure (PP) >60 mm Hg.
- Evaluation of interventions is needed that might prevent or reverse the decrease of vascular compliance in patients with increased pulse pressure (PP).
- The validity of the semi-quantitative estimation of vascular calcification as a predictor of survival requires confirmation in other centers. Evaluation of alternative methods for estimation of coronary artery calcification (e.g., multislice CT) is needed.

Section III. State of the Science: Novel and Controversial Topics in Cardiovascular Diseases

Intradialytic Hypotension

Research Recommendations

- A randomized study in patients with intradialytic hypotension (IDH) is needed to assess the safety, efficacy, and cost-effectiveness of automated feedback systems that continuously adjust ultrafiltration rate, dialysate sodium, and dialysate temperature.
- Controlled studies are also needed to examine the use of continuous on-line hematocrit monitoring to calculate the rate of ultrafiltration and blood volume and impedance measurements in the assessment of actual dry weight and desired goal for ultrafiltration.

Troponin

Research Recommendations

- A prospective, randomized clinical trial on troponin testing and clinical decision-making would provide valuable information.
- There is a need for prospective cohort studies on the correlation between troponin levels and the burden of Coronary Artery Disease (CAD), as well as

fatal and nonfatal CAD-related and non-CAD-related events.

Inflammation

Research Recommendations

- Future research should aim at finding the optimal "cut-off" point at which elevated C-reactive protein (CRP) predicts outcome in CKD.
- Studies are needed to investigate the possible interactions between the presence of inflammation and both traditional risk factors (such as dyslipidemia) and nontraditional risk factors (such as oxidative stress, vascular calcification, advanced glycation end-products and endothelial dysfunction) for atherosclerosis.
- Research is also required to investigate the impact of age, gender, physical activity, diet, race and genetic factors on the prevalence of inflammation in CKD.
- Nonpharmacological and pharmacological interventions for patients with signs of inflammation should be developed and evaluated for efficacy in reducing inflammation and improving clinical outcomes in this patient group.
- The independent role of potential proatherogenic inflammatory biomarkers such as CRP, fetuin-A, and interleukin-6 (IL-6), in the processes of atherogenesis and progression, need to be tested in the uremic milieu.

Oxidative Stress

Research Recommendations

- Studies are needed to determine which surrogate marker of oxidative stress best predicts outcome in CKD patients.
- Further research is required to investigate the possible interactions between the presence of oxidative stress and both traditional risk factors (such as dyslipidemia) and non-traditional risk factors (such as inflammation, vascular calcification, advanced glycation end-products and endothelial dysfunction) for atherosclerosis.
- Studies are also needed to determine which oxidative stress pathway (i.e., nitrosative, chlorinated or carbonyl stress) is quantitatively the most important in CKD patients. Nonpharmacological (such as diet) and pharmacological (such as vitamin E and acetylcysteine) interventions for CKD patients with signs of increased oxidative stress should be developed and evaluated for efficacy in reducing oxidative stress and improving clinical outcomes in this patient group.

Omega-3 Fatty Acids

Research Recommendations

- Studies are required to identify the essential fatty acid status of CKD patients, both progressive and for those on renal replacement therapy.
- Studies should also evaluate the interrelationships among ω-3 fatty acid supplementation, oxidative stress, CVD and dialysis therapy.
- Clinical trials are needed to evaluate the role of dietary fatty acid modification on CVD risk and outcomes in CKD patients on renal

replacement therapy.
- Further clinical trials should evaluate current nutrition recommendations for the general population modified to the diet recommendations for CKD patients.

Homocysteine

Research Recommendations

- Further data are required regarding the effect of vitamin therapy on clinical outcomes.
- Lipoprotein(a) (Lp(a)) and Apolipoprotein(a) (Apo(a)) Polymorphism
- Further large dialysis cohorts should investigate the value of Lipoprotein(a) (Lp(a)) concentrations and Apolipoprotein(a) (Apo(a)) phenotypes for risk assessment. This question should especially be addressed in PD patients as well as in various ethnicities.
- A possible interaction of various Apolipoprotein(a) (Apo(a)) isoforms with lipids and other cardiovascular risk factors should be investigated.
- Experimental therapeutic strategies to lower Lipoprotein(a) (Lp(a)) should be examined in randomized, controlled clinical trials, especially in high-risk populations such as dialysis patients.

Malnutrition

Research Recommendations

- Studies are needed to identify the incidence of hypoalbuminemia due to visceral protein store depletion vs. hypoalbuminemia due to chronic inflammation.
- Effective nutrition and medical management interventions need to be identified that are specific for malnutrition vs. inflammation vs. metabolic challenges.
- Studies are also required to examine how long-term nutritional intervention affects cardiovascular risk and specific risk factors for accelerated atherosclerosis, such as oxidative stress and endothelial dysfunction, in CKD patients.

Family History and Genetics

Research Recommendations

- The predictive value of family history of CVD should be investigated in patients with renal disease.
- Further large dialysis cohorts should investigate the value of Lipoprotein(a) (Lp(a)) concentrations and Apolipoprotein(a) (Apo(a)) phenotypes for risk assessment. This question should especially be addressed in PD patients as well as in various ethnicities. Arising candidate genes for CVD should be investigated in dialysis patients.

Menopause

Research Recommendations

- Little is known regarding cardiovascular outcomes associated with menopause. Observational studies should assess the impact of menopause on CVD risk. Given that there are over 30,000 women with CKD treated with hormone replacement therapy (HRT), studies should assess if the use of HRT is associated with improved CVD outcomes.

Preventive Foot Care in Diabetes

Research Recommendations

- Long-term studies are warranted to examine the effectiveness of screening with ABI, and early diagnosis of peripheral vascular disease (PVD), on reducing the development of critical limb ischemia and the rates of amputation.
- Randomized, controlled trials are needed to study the effects of antiplatelet agents and statins in asymptomatic and symptomatic PVD on the development of critical limb ischemia and the rates of amputation.

Aspirin

Research Recommendations

- Randomized controlled trials of aspirin as primary or secondary prophylaxis in preventing cardiovascular events with attention to GI bleeding are warranted.
- The cost-effectiveness of aspirin (risk of GI bleeding versus reduction in cardiovascular events) needs to be studied.

Guideline 2: Evaluation of Patients with CKD or Hypertension

Research Recommendations

The current clinical questions related to essential hypertension are all areas that require further research in CKD. These questions cannot be answered unless patients with CKD are included in large randomized trials. Areas for investigation include:

- Studies on the effect of various clinical and genetic factors on the response to antihypertensive therapy, to determine what factors should be included in the evaluation.
- Studies on the relationship between levels of proteinuria and albuminuria, to simplify the detection, evaluation and management of CKD.
- Studies on the cost-effectiveness of various components of the evaluation and the frequency of follow-up.

Guideline 3: Measurement of Blood Pressure in Adults

Research Recommendations

There are many unanswered questions related to the measurement of blood pressure in the CKD population.

- Research should specifically be performed in the patients with CKD who have been documented to have abnormal vascular compliance, to determine if oscillometric monitors for casual measurements give accurate results. If differences are noted, oscillometric normal values should be developed as they were for ambulatory blood pressure monitoring (ABPM).
- Controlled trials need to be performed to determine if blood pressure management in CKD patients with ambulatory blood pressure monitoring (ABPM) is superior to casual blood pressure (CBP) guided therapy.
- More research into the prognostic ability of self-monitored blood pressure (SMBP) is needed. A systematic attempt should be made to test all home blood pressure monitors for accuracy especially when used for patients with CKD.
- Should all patients with CKD, especially those with higher stages of CKD have ambulatory blood pressure monitoring (ABPM), even if normotensive, to determine the presence of dipper status?
- Does white-coat hypertension (WCH) predispose to sustained hypertension?
- Should the definition of white-coat hypertension (WCH) take into account sleep blood pressure measurements for CKD patients?
- The data that alterations in circadian blood pressure rhythms are related to end-organ damage are strong, but would they benefit from a large multicenter study in CKD characterized by CKD stages?
- Does the normalization of circadian blood pressure pattern confer any

protection? How would this be accomplished? Are some antihypertensive agents superior in this regard? What should be the dosage timing?
- More research using ambulatory blood pressure monitoring (ABPM) to adjust antihypertensive therapy is required. Research into the mechanisms of the abnormal blood pressure patterns coupled to the increase in end-organ damage is required and may lead to the development of new therapies.

Guideline 4: Evaluation for Renal Artery Disease

Research Recommendations

- A long-term, randomized controlled trial (RCT) should be conducted to compare the effect of medical management versus percutaneous transluminal renal angioplasty (PTRA) with stenting on blood pressure control, progression of kidney disease, and cardiovascular morbidity and mortality. Such a trial should aim to answer the questions of who is the ideal candidate for interventional therapy, and what are the benefits, if any, of an invasive approach to renal artery disease (RAD).
- The clinical predictive index needs to be validated in a hypertensive population composed of African American, Hispanics, and native Americans as well as Caucasians.

Guideline 5: Education on Self-Management Behavior

Research Recommendations

It is necessary to establish optimal interventions that combine behavioral approaches with pharmacological therapies to reduce risk factors for hypertension. Particular attention must be paid to identifying which behavioral strategies are most effective in producing desired behavior change.

- Research should be done with the CKD population that relates to behavioral factors implicated in an individual's management of hypertension. This research should include lifestyle factors, such as obesity, alcohol, cigarette smoking, and inactivity; social and environmental variables, such as lack of social support, socioeconomic status, and ethnicity; and individual characteristics, such as personality and reaction to stress.
- Research is needed regarding effective strategies for maintaining long-term adherence to self-care requirements for prevention and treatment of hypertension.
- Research is needed regarding the most effective strategies for promoting self-management behavior in minority populations.
- The effect of low-dose, combination therapy on adverse effects of medication and, in turn, medication adherence, should be examined.

Guideline 6: Dietary and Other Therapeutic Lifestyle Changes in Adults

Research Recommendations

- Conduct randomized, controlled trials to determine optimal dietary patterns to reduce blood pressure and slow the progression of kidney disease.
- Perform research to determine the effects of sodium reduction on blood pressure in patients with CKD.
- Conduct outcome studies to determine the effectiveness and value of Medical Nutrition Therapy (MNT) in CKD.

Guideline 7: Pharmacological Therapy: Use of Antihypertensive Agents in CKD

Research Recommendations

- Additional clinical studies are needed on the treatment of hypertension in patients with CKD. The variation in blood pressure within the population and the time-to-time variation in blood pressure within an individual need to be determined to permit definition of the blood pressure goal for the population.
- The effect of blood pressure control on rates of CVD in patients with CKD needs to be ascertained.
- A comparison of the effects of different antihypertensive agents on cardiovascular events in patients with CKD needs to be determined.

Guideline 8: Pharmacological Therapy: Diabetic Kidney Disease

Research Recommendations

The following questions require additional study in diabetic kidney disease:

- What is the optimal dose of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) for kidney disease protection?
- What is the possible protective role of ARBs and other classes of antihypertensive agents, either alone or in combination with ACE inhibitors, on slowing kidney disease progression and CVD?
- The question regarding the optimal level of blood pressure reduction for cardiovascular risk reduction will be answered in 2008 by the Anemia Correction in Diabetes (ACORD) trial. However, this may not answer the question about the optimal level of blood pressure to slow diabetic kidney disease progression.
- Finally, studies are needed to examine the relationship between magnitude of albuminuria reduction and reduction in kidney disease progression and CVD risk, and to determine the optimal "target value" for urine albumin excretion in diabetic kidney disease during treatment with ACE inhibitors and ARBs.

Guideline 9: Pharmacological Therapy: Non-Diabetic Kidney Disease

Research Recommendations

Recommended areas for future research include:

- Optimal dosage of ACE inhibitor therapy for kidney disease protection; potential protective effects of ARBs and other classes of antihypertensive agents, either alone or in combination with ACE inhibitors, on slowing kidney disease progression;
- Preferred agents for to slow kidney disease progression in patients without proteinuria.
- Optimal level of blood pressure control for various levels of protein excretion; development of more discriminating diagnostic techniques for differentiating between types of nondiabetic CKD;
- Optimal level of proteinuria to slow kidney disease progression ("proteinuria-guided therapy").

In all studies, if feasible, it would be preferable to focus on specific types (diagnoses) of CKD due to causes other than diabetes.

Guideline 10: Pharmacological Therapy: Kidney Disease in the Kidney Transplant Recipient

Research Recommendations

- Most kidney transplant recipients have CKD after transplantation. Kidney transplant recipients are an ideal population in which to study the effects of antihypertensive therapy on the progression of kidney disease and the risk of CVD. In these patients, the onset of kidney disease in the transplanted kidney is known, patients are treated in specialized centers, measurements of blood pressure and urine protein can be standardized by adherence to protocols, and study endpoints such as deterioration in GFR and graft loss are well defined.
- The relationship of immunosuppressive medications to levels of blood pressure, proteinuria, progression of CKD, and clinical CVD also needs to be studied. For example, the use of calcineurin-inhibitors impacts the development and severity of posttransplantation hypertension. The effect of antihypertensive agents may be different depending on the immunosuppressive regimen. When using protocols that avoid or minimize exposure to calcineurin inhibitors, the value of dihydropyridine calcium-channel blockers may not be as important.
- Finally, ambulatory blood pressure monitoring should be studied in this population since a disturbed day-night blood pressure rhythm is present and office blood pressure may not accurately reflect the burden of hypertension and its relationship to progression of kidney disease or CVD.

Guideline 11: Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in CKD

Research Recommendations

- Additional clinical studies are needed for the treatment of hypertension using ACE inhibitors and ARBs in patients with CKD due to glomerular diseases.
- More studies are required with co administration of ACE inhibitors and ARBs.
- The specific dose of ACE inhibitors or ARBs that confers the optimum renoprotective effect remains unclear.
- Future controlled trials will need to compare the dose-response relationship of antihypertensive agents to their adverse effects in patients with CKD.
- Studies should also be designed to determine differences between agents of the same class and among agents from different classes.
- Epidemiological studies will need to determine risk factors for adverse event formation.

Guideline 12: Use of Diuretics in CKD

Research Recommendations

- Additional clinical studies are needed to determine whether differences exist amongst the various loop diuretics in how each influences blood pressure independent of volume loss.
- Moreover, additional studies are needed to determine if the blood pressure-lowering response to a loop diuretic is better with ACE inhibitors or ARBs.
- Future controlled trials will need to explore the relationship between CKD progression and the electrolyte changes that accompany loop diuretic administration.
- Studies should also be designed to evaluate the impact on calcium-phosphate balance and the triggering of secondary hyperparathyroidism from the hypercalciuria produced by loop diuretic treatment.
- Finally, more studies are needed with combination loop and thiazide diuretic therapy to determine if this is a more effective and/or safer approach than high-dose therapy with a loop diuretic alone and to determine which is the best thiazide diuretic to combine with a loop diuretic.

Guideline 13: Special Considerations in Children

Research Recommendations

- Studies to investigate the role of blood pressure management in children with CKD on progression of CKD and CVD need to be undertaken so that appropriate recommendations can be formulated.
- There is a major lack of studies to address the role of adequate blood pressure management in children with CKD, on progression of kidney disease, and on CVD.
- Further studies of hypertension in CKD in children should include ABPM. It is a valuable clinical tool that can provide additional information about the alterations in blood pressure patterns observed in CKD and the prediction of CVD.

KDIGO (Kidney Disease: Improving Global Outcomes) published a 2012 update to the 2002 NKF-KDOQI guideline for evaluation, classification, and stratification of chronic kidney disease (CKD). NKF-KDOQI convened a work group to write a commentary on the KDIGO guideline in order to assist US practitioners in interpreting the KDIGO guideline and determining its applicability within their own practices. Overall, the commentary work group agreed with most of the recommendations contained in the KDIGO guidelines, particularly the recommendations regarding the definition and classification of CKD. However, there were some concerns about incorporating the cause of disease into CKD classification, in addition to certain recommendations for evaluation and management. Recommendations for further research presented within the KDIGO guideline are as follows.

Research Recommendations

Chapter 1

- Extensive work by the CKD Prognosis Consortium has defined the RRs across GFR and albuminuria categories for several important outcomes, including all-cause mortality, CVD, and kidney failure (Figures 6 and 7). Risk increases incrementally in both directions - down the GFR categories and across the albuminuria categories. Levels of risk can be identified and grouped into categories, but they may differ somewhat for each outcome. Additional research is needed to map these GFR and albuminuria categories and cause of kidney disease to other important outcomes of CKD

- Testing for proteinuria using a urine albumin rather than total protein first-line approach may occasionally miss cases of tubular proteinuria but the significance of this problem is probably overestimated and should be the subject of further research.

Chapter 2

- We recommend further research to more accurately define the frequency with which GFR and albuminuria measurements should be performed based on their ability to inform strategies which prevent adverse outcomes (e.g., progression of kidney disease and death).

- With respect to the impact of changes in albuminuria over time, preliminary analysis of cohort studies is limited and suggests that further research is required to more accurately determine the change in albuminuria associated with an increased risk of kidney disease progression.

- We recommend research to confirm rates which can be classified as slow, moderate, and rapid progression of kidney disease. The rate to define ‘‘rapid progression’’ may vary depending on the outcome considered, such as kidney failure versus mortality for example. It will be important for researchers to determine methods by which reproducible classification systems for describing rates of progression can be developed.

- Existing CKD risk prediction models demonstrate the potential and the capabilities of developing clinically meaningful classification of risk for individual patients; however, they require validation in future studies. Further research is required to establish whether prediction formulas may differ for different ethnicities. Further research is required to determine which formula best predicts who will have progressive increases in albuminuria and progressive decreases in GFR. The key components of prediction equations for ESRD may well be different than prediction equations for cardiovascular events or death.

Chapter 3

- Prospectively designed clinical studies with a clear and uniform definition of CKD and AKI and adjusted for comorbidities are needed to determine the: K frequency of AKI events in a CKD population; K outcome of AKI in patients with CKD; K importance of proteinuria in addition to low GFR in the risk of AKI.

Chapter 4

- National and international research groups, and those with CKD-focus organizations (International Society of Nephrology, International Federation of Kidney Foundations, and other national bodies) should ensure adequate representation of people with CKD in clinical trials, leading to an improved understanding of pharmacodynamics of those with CKD.

- There is a need for more research into simple preventative measure such as pre-investigation rehydration (see below). There has not previously been a universal definition for AKI following administration of contrast media. However, recommendations from the KDIGO AKI Guideline suggest that the same general AKI definition and staging be used for changes in kidney function, irrespective of etiology.

- Prospective studies using direct measures of GFR before and after administration of radiological contrast media are required to help define the incidence of AKI. Such studies would also be able to validate creatinine or other estimates of GFR in people undergoing radiological investigation. Prospective controlled trials of rehydration using different fluids (saline, bicarbonate, Hartmann's) and validated estimates of GFR are urgently required. Definitive studies of N-acetylcysteine and other antioxidants would help determine their usefulness or otherwise.

- As for iodinated contrast media, a prospective study of people with CKD undergoing nuclear MRI with gadolinium contrast would help define change in GFR and validate estimators. Because NSF is such a serious condition, an RCT of dialysis in people with GFR o30 ml/min/1.73 m2 would help to determine risk-benefit in these patients, though recruitment may be difficult due to potential ethical concerns.

- Prospective study in people with normal renal function and those with different severities of CKD are urgently required in order to define the acute biochemical and metabolic effects of phosphate-containing bowel preparations. There is also a need for a study of all people undergoing bowel preparation with whatever preparation in order to explore the effects on GFR on the incidence of this complication. More definitive exploration of rehydration therapy (type and volume) in people with CKD undergoing bowel preparation is urgently needed.

- Prospectively designed clinical studies with a clear and uniform definition of CKD and AKI and adjusted for comorbidities are needed to determine: K the frequency of AKI events in a CKD population K the outcome of AKI in patients with CKD condition Kidney International Supplements (2013) 3, 91–111 109 chapter 4K the importance of proteinuria in addition to low GFR in the risk of AKI.

Guideline 1: Definition and Stages of Chronic Kidney Disease

Research Recommendations

- The Workgroup acknowledges that the proposed definition and classification chronic kidney disease and stages is arbitrary and can be refined by further research.
- The normal range for glomerular filtration rate (GFR) was defined using a relatively small number of individuals. It would be useful to conduct a large cross-sectional study of GFR in general population, across the full range of age, gender, race, ethnicity, protein intake, with adjustment for other factors, including high blood pressure, diabetes, and other conditions that affect GFR. This study would permit validation of prediction equations based on serum creatinine or other filtration markers within the normal range of GFR.
- The outcomes of individuals with various stages of chronic kidney disease are not defined. A cohort study of patients with chronic kidney disease would enable definition of the relationship between factors and outcomes of stages of chronic kidney disease. This would be particularly useful in defining the relationships among stages of chronic kidney disease, progression of chronic kidney disease, initiation and progression of cardiovascular disease, health service utilization, and barriers to care.
- Age-related rise in blood pressure and decline in GFR may be responsible for a large number of individuals in Stage 3 (GFR 30 to 59 mL/min/1.73 m2). There are even more individuals with high blood pressure and decreased GFR (GFR 60 to 89 mL/min/1.73 m2), who have not been classified as having chronic kidney disease. It would be useful to conduct cross-sectional and cohort studies of elderly individuals with normal and abnormal blood pressure and GFR to assess the effect of high blood pressure and decreased GFR in this population.

Guideline 2: Evaluation and Treatment

Research Recommendations

- Much research is needed to define diagnostic and therapeutic strategies to reduce adverse outcomes of chronic kidney disease at each stage of disease. It will also be important to assess the effect of implementing these guidelines on the outcomes of chronic kidney disease.

Guideline 3: Individuals at Increased Risk of Chronic Kidney Disease

Research Recommendations

- Implementation of these guidelines will require education of all health care providers about risk factors for chronic kidney disease and methods of testing. The Seventh Report of the Joint National Committee for the Prevention, Evaluation, Detection and Treatment of High Blood Pressure (JNC-VII) and the American Diabetes Association have issued recommendations for the evaluation of patients with high blood pressure and diabetes, respectively, for chronic kidney disease. However, as indicated in Table 42, a large number of individuals without high blood pressure and diabetes may also be at increased risk. Thus, it will be important to test a larger population than currently targeted, which would increase the cost of health care.
- The increased health care costs that would follow implementation of a screening program for chronic kidney disease may well require a more solid base of evidence than is currently available. The Work Group recommends development of a clinical practice guideline focused on this issue in order to develop specific recommendations for evaluating adults for chronic kidney disease. In the past, universal screening was not recommended because of the low prevalence of chronic kidney disease and the lack of treatments to improve outcomes. Data provided in these guidelines suggests that the prevalence of earlier stages of chronic kidney disease is higher than previously known and that earlier detection and treatment to prevent or delay the loss of kidney function and development of cardiovascular disease in chronic kidney disease. If sufficient information is not available to assess the value of testing individuals at increased risk, or of universal screening, the Work Group suggests that research on evaluation programs should be conducted.

Guideline 4: Estimation of GFR

Research Recommendations

Estimating GFR

- Although existing equations based on serum creatinine provide an excellent cost-effective method for estimating GFR, their precision is limited. New methods are needed, particularly for detecting mild and moderate kidney disease, but their value in terms of bias, precision, and practicality should be well tested in large samples of subjects with and without kidney disease. In adults, new measures will have to perform substantially better than the 12.1% median difference (~90% of estimates within 30%) from GFR obtained with serum creatinine, age, sex, and race using the MDRD Study equation. In children, standardization of creatinine measurement across studies, use of gold standard GFR measures for reference, and inclusion of larger samples of children of different ages and ethnicities will allow refinement of the constants which should be used in estimating GFR in future modifications of the Counahan-Barratt or Schwartz formula.

- While the MDRD Study equation has many advantages, it needs further validation. In particular, further studies should focus on individuals with diabetes, mild decreases in kidney function or normal GFR, Mexican-Americans (whose average serum creatinine is lower than Caucasians), and non-US populations. The extent to which averaging multiple estimates improves precision needs further study. Including a direct measure of body composition by bioelectric impedance or dual-energy X-ray absorptiometry scanning may provide promising directions for improving on the prediction of GFR using serum creatinine.

Definition of "Normal" GFR Across Ages and Ethnicities

- The definition of decreased GFR relies on an understanding of the "normal" GFR range. The amount of data in healthy individuals of different ethnicities and children is limited. GFR may differ across ethnic groups but data are very sparse. It is also unknown to what extent a mild decrease in GFR among individuals without hypertension is indicative or kidney disease or "normal" aging.

Prediction Equations for Creatinine Excretion

- It would be useful in clinical practice to be able to estimate creatinine excretion from physiologic variables related to creatinine generation and extra-renal elimination, such as age, gender, race, body size, and GFR. This might be done in cross-sectional studies that measured these physiologic variables as well as 24-hour urine creatinine excretion. This would allow improved estimates of daily excretion of some urine solutes from measurements of solute-to-creatinine ratio in spot urine samples. estimates of daily excretion of some urine solutes from measurements of solute-to-creatinine ratio in spot urine samples.

Guideline 5: Assessment of Proteinuria

Research Recommendations

- Evaluate novel approaches to measuring urine and blood abnormalities which may predate and possibly predict proteinuria/albuminuria. Examples include elevated levels of beta -2-microglobulin and other tubular proteins in the urine of diabetic patients. Additional efforts should be instituted to identify constituents present in blood and/or urine that indicate normal kidney function with high specificity.
- It would be useful to conduct prospective trials of the long-term efficacy of antihypertensive medications that reduce albumin/protein excretion in kidney disease. These studies should incorporate better procedures to examine the efficacy of sustaining kidney function in advanced kidney disease and in reducing the incidence of cardiovascular disease in patients with kidney disease.

- It would also be useful to determine the relationships between factors that may affect albumin/protein excretion and also increase the risk of macrovascular disease (eg, glucose intolerance/diabetes mellitus, rising blood

pressure, elevated lipid levels, and obesity) and progressive kidney failure.

Guideline 6: Markers of Chronic Kidney Disease other than Proteinuria

Research Recommendations

- Novel and expanded uses of established methodologies (such as Doppler or functional MRI) should be pursued in clinical research studies. Several novel urinary markers show promise of noninvasive demonstration of kidney damage or prediction of disease progression. None appears to be ready at this time for widespread application in clinical practice. Longitudinal and follow-up studies are necessary to verify whether abnormal NAG and possibly retinol-binding protein excretion in normoalbuminuric diabetic patients reliably predict later development of microalbuminuria and diabetic nephropathy. Similar studies are needed to confirm whether increased beta-2-microglobulin excretion predicts development of kidney failure in patients with idiopathic membranous nephropathy. Longitudinal studies of urinary excretion of specific cell types (macrophages, natural killer (NK) cells, podocytes) in diabetic nephropathy, Henoch-Schönlein nephropathy, and IgA nephropathy are also necessary in order to confirm preliminary findings that cyturia is strongly associated with activity in these diseases. Preliminary work on the urinary excretion of podocyte-specific marker proteins such as podocalyxin and nephrin should be validated by further studies.

Guideline 7: Association of Level of GFR with Hypertension

Research Recommendations

- A broad set of recommendations for research on high blood pressure in chronic kidney disease was developed by the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease. Recommendations for observational studies are reproduced in Table 74 and for clinical trials in Table 75.

Guideline 8: Association of Level of GFR with Anemia

Research Recommendations

Clearly, more information is needed on hemoglobin levels in chronic kidney disease—especially in patients in the early stages of kidney disease and as kidney function declines. Future studies should include:

- Evaluation of the relationships between erythropoietin levels, hemoglobin and iron stores in patients with chronic kidney disease at each stage of the disease
- Description of changes in these hematological parameters in specific subgroups, such as diabetics and patients with failing transplant grafts
- Evaluation of the impact of treatment of anemia in stages of kidney disease prior to dialysis (CKD Stages 1-4) on kidney function decline, cardiac

function, and general well-being
- Economic evaluations of therapeutic strategies which include maintenance of hemoglobin versus correction from low levels at different stages of chronic kidney disease.

Guideline 9: Association of Level of GFR with Nutritional Status

Research Recommendations

- Although the data presented herein is compelling, more research, especially prospective studies evaluating the impact of kidney disease on nutritional parameters, is needed. Importantly, studies to define the optimal methods to evaluate nutritional status in chronic kidney disease patients are critical. Prospective studies evaluating the impact of different levels of nutritional status on subsequent outcome in chronic kidney disease patients should also be performed. Finally, prospective studies evaluating the impact of intensive nutritional counseling on nutritional status and possibly clinical outcome in chronic kidney disease patients should be carried out.

Guideline 10: Association of Level of GFR with Bone Disease and Disorders of Calcium and Phosphorus Metabolism

Research Recommendations

- Much of the available information regarding abnormalities of mineral metabolism is derived from studies of patients with kidney failure or severely decreased kidney function. Clearly, more information is needed on the abnormalities of bone mineral metabolism among patients with earlier stages of chronic kidney disease. Moreover, research on outcomes related to abnormal mineral metabolism or bone disease is lacking in both patients with mildly, as well as severely decreased kidney function. In addition to bone complications, there is increasing evidence relating abnormal calcium-phosphorus metabolism and hyperparathyroidism to vascular calcification and cardiovascular complications.
- The relationship between levels of the available markers, and levels of kidney function, should be more accurately characterized. In addition, the relationship between such levels and kidney function should be separately studied among patients with additional risks of bone complications, that is, patients treated for prolonged periods with corticosteroids and transplant recipients.
- Research should also focus on the impact of interventions on levels of available markers and outcomes, specifically of interest would be comparing patients cared for by nephrologists with those not under the care of nephrologists, patients treated for some specified period of time for hyperparathyroidism compared to those not treated, and patients treated with corticosteroids compared to those never treated with such drugs.

Guideline 11: Association of Level of GFR with Neuropathy

Research Recommendations

- Much of the available information regarding neuropathy is derived from studies of patients with kidney failure. More information on neuropathy among patients with chronic kidney disease with earlier stages of chronic kidney disease may provide other means to follow progression of chronic kidney disease. In addition, if neuropathy were to be more carefully described and noted to have a high prevalence in earlier stages of chronic kidney disease and a relationship to kidney function, treatments to delay its progression could be considered.
- The relationship between subjective and objective measures of neuropathy, and levels of kidney function, should be more accurately characterized. In addition, the relationship between neuropathy and kidney function should be separately studied among patients with additional risks of neuropathy, such as diabetics and patients with amyloidosis.

Guideline 12: Association of Level of GFR with Indices of Functioning and Well-Being

Research Recommendations

- Research in dialysis patients has shown that functioning and well-being pre-treatment may predict post-treatment outcomes. Therefore, large-scale longitudinal studies are needed to evaluate the relationship between GFR and all domains of functional status and well-being throughout the course of progression of kidney disease. More research should be undertaken using the recommended standardized instruments and their outcomes compared. Whenever specific medications could affect outcomes, usage should be assessed. Because conditions such as anemia, bone disease, cardiovascular, disease, and diabetes can affect functioning and well-being, researchers need to study whether appropriate management of these conditions improves functioning and well-being.
- Finally, researchers need to examine the effectiveness of rehabilitation interventions in earlier stages of chronic kidney disease. Doing so could provide further scientific evidence for the relationship of kidney function and treatment on patients' risk of dysfunction, hospitalization, and death and increase understanding of what interventions improve functioning and well-being and reduce the burden of chronic kidney disease on the patient, his or her family, and society.

Guideline 13: Factors Associated with Loss of Kidney Function in Chronic Kidney Disease

Research Recommendations

- It is evident that there is a large amount of data in studies of varying size and quality regarding the impact of underlying conditions, patient characteristics, and interventions. However, there are certain factors whose impact has not been conclusively determined, such as dietary protein intake, hyperlipidemia,

and anemia and their treatment. Proteinuria as a risk factor deserves special consideration. Antihypertensive agents, especially ACE-inhibitors and angiotensin-receptor blockers, reduce proteinuria and slow the progression of kidney disease. However, the role of proteinuria per se has not been adequately studied. There is a need to develop alternative therapies to reduce urine protein.

- Many of the conclusions regarding the impact of factors unrelated to intervention, such as age, gender, race, and cause of kidney disease, come from "small" interventional trials. Similarly, in the case of the impact of blood pressure control, conclusions largely come from the observations that patients with lower blood pressures have improved outcomes. In the case of cause of kidney disease, the conclusion that certain causes are associated with faster rates of progression come from the comparison of studies of single causes, using diverse methods to measure or estimate GFR. A noninterventional prospective cohort study including sufficient numbers of patients with all causes of kidney disease, undergoing similar testing for level of kidney function, would be ideal to evaluate the impact of cause of kidney disease on the rate of decline in GFR. Alternatively, a sufficiently large prospective interventional trial could achieve a similar goal.

Guideline 14: Association of Chronic Kidney Disease with Diabetic Complications

Research Recommendations

- Much of the understanding about the relationships between diabetic nephropathy and cardiovascular disease, retinopathy, and neuropathy comes from studies in Caucasians. Yet the epidemic of diabetes affects many racial/ethnic groups worldwide. Since race/ethnicity may influence not only the risk of diabetes, but the severity and type of diabetic complications that develop, further characterization of the impact of diabetes in different populations is needed. Further characterization of these relationships in the elderly is also needed. Moreover, the extent to which aggressive treatment of diabetic complications modulates the progression of kidney disease needs to be examined, since recent studies suggest that improvements in the treatment of cardiovascular disease in patients with type 2 diabetes have contributed to an increase in diabetic kidney failure.

Guideline 15: Association of Chronic Kidney Disease with Cardiovascular Disease

Research Recommendations

- A large prospective multi-ethnic cohort study involving patients with Stage 3 and 4 chronic kidney disease is necessary to further examine the impact of "traditional" and "kidney disease-related" risk factors on incident cardiovascular disease. Emphasis should be placed on the recognition of potentially modifiable risk factors. Such a study could also determine the time course of cardiovascular disease in the chronic kidney disease population.

- A predictive clinical tool, using kidney disease stage and diagnosis, risk factors, and/or other variables, should be developed to better predict risk in patients with chronic kidney disease.
- Standards for the measurement of kidney function and albuminuria in observational and controlled trials should be established.

Research Recommendations

There are reasonable doubts as to whether trial results from the general population are applicable to all patients with CKD. It is beyond the scope of these guidelines to recommend all research that should be conducted in patients with dyslipidemia and CKD, or to design clinical trials. However, it is apparent that some questions are particularly well suited for study (Table 42), although these recommendations are not meant to be endorsements for specific protocols.

Table 42. Intervention Trials That Are Needed in Patients with Chronic Kidney Disease.

Population	Primary Intervention	Lipid Profile	Primary Endpoints
Stages 1-4 CKD	Statin	Any lipid profile, or ↑ LDL	ACVD, and/or Decline in GFR
Stages 1-4 CKD	Fibrate	↑ Triglycerides with ↑ non-HDL cholesterol	ACVD, and/or Decline in GFR
Hemodialysis	Statin, or Sevelamer hydrochloride	Any lipid profile	ACVD
Hemodialysis	Statin, or Fibrate, or Sevelamer hydrochloride	↑ Triglycerides with ↑ non-HDL cholesterol	ACVD
Peritoneal Dialysis	Statin	Any lipid profile, or ↑ LDL	ACVD
Transplant	Statin	Any lipid profile, or ↑ LDL	ACVD, and/or Decline in GFR

For children with CKD and/or a functioning kidney transplant, prospective cohort studies with long-term follow-up are recommended to determine:

- The prevalence of dyslipidemias at all stages of CKD over time
- The associations between dyslipidemias and subsequent ACVD

For children with CKD and/or a functioning kidney transplant, phase I and phase II trials, and pharmacokinetic dosing studies are recommended to establish the safety and lipid-lowering efficacy of agents (*including, but not limited to*):

- Bile acid sequestrants, eg, colesevelam
- Cholesterol uptake inhibitors, eg, ezetibmide
- Statins
- Fibrates
- Nicotinic acid
- Sevelamer hydrochloride
- Appropriate lipid-lowering drug combinations

For adults with CKD and/or a functioning kidney transplant, phase I and phase II trials and pharmacokinetic dosing studies are recommended to establish the safety and lipid-lowering efficacy of new agents (*including, but not limited to*):

- Colesevelam
- Cholesterol uptake inhibitors, eg, ezetimibe
- Appropriate lipid-lowering drug combinations

For patients with Stages 1-4 CKD, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the rate of decline in GFR in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with LDL 100 mg/dL (2.59 mmol/L).
- A statin safely reduces the rate of decline in GFR in patients with LDL 100 mg/dL (2.59 mmol/L).
- A fibrate safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides 200 mg/dL (2.26 mmol/L) and non-HDL cholesterol 130 mg/dL (3.36 mmol/L).
- A fibrate safely reduces the rate of decline in GFR in patients with triglycerides 200 mg/dL (2.26 mmol/L) and non-HDL cholesterol 130 mg/dL (3.36 mmol/L).

For chronic hemodialysis patients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides 200 mg/dL (2.26 mmol/L) and non-HDL cholesterol 130 mg/dL (3.36 mmol/L).
- A fibrate safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides 200 mg/dL (2.26 mmol/L) and non-HDL cholesterol 130 mg/dL (3.36 mmol/L).
- Sevelamer hydrochloride safely reduces the incidence of ACVD and all-cause mortality in patients with triglycerides 200 mg/dL (2.26 mmol/L) and non-HDL cholesterol 130 mg/dL (3.36 mmol/L).

For chronic peritoneal dialysis patients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with LDL 100 mg/dL (2.59 mmol/L).

For kidney transplant recipients, these and other appropriate studies are recommended to determine whether:

- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with any lipid profile.
- A statin safely reduces the rate of decline in GFR in patients with any lipid profile.
- A statin safely reduces the incidence of ACVD and all-cause mortality in patients with LDL 100 mg/dL (2.59 mmol/L).
- A statin safely reduces the rate of decline in GFR in patients with LDL 100 mg/dL (2.59 mmol/L).

Guideline 1: Initiation of Dialysis

Research Recommendations

- Although it is recognized that the patient's clinical condition at the start of Kidney Replacement Therapy (KRT) is an important predictor of outcome, there are no data to confirm whether an "earlier" (in terms of kidney progression) or a "healthier" (less advanced comorbidities) start results in a survival advantage or just a lead-time bias. Furthermore, is the answer to that question dependent on prior rate of progression of kidney disease, cause of kidney disease, the same for different ethnic groups, or dependent on comorbidities present? Given the cost of Kidney Replacement Therapy (KRT) to society, it is important to know whether, in general, the timing of the start of dialysis therapy improves total lifespan or only increases time on dialysis therapy, but not total lifespan. If it is the latter, data to show that the patient otherwise would tend to be healthier with less hospitalization, better QOL, or rehabilitation also would be important to know.
- Much more research is needed regarding the impact on the patient of the period leading up to dialysis therapy and the period just after starting dialysis therapy. Additional research is needed on mood disorders, particularly depression and anger, that may develop during this period and the impact such disorders may have on outcomes after dialysis therapy is initiated.

Guideline 2: PD Solute Clearance Targets and Measurements

Research Recommendations

- It now is well documented that the presence of RKF offers the typical patient on Kidney Replacement Therapy (KRT) an important survival advantage. What is not known is why that is true. Is it caused by better blood pressure or volume control, more small-solute removal, removal of middle molecules, or some other poorly recognized function of metabolic or paracrine function of the kidney tubules? Additional research to define the effects of RKF would be most important. Results may influence clinical practice, guidelines on initiation of dialysis therapy (can it be done in an incremental manner?), and further determine how one best includes the residual kidney component of total solute clearance in dose calculations.
- As noted in the text of these guidelines, 2 recent prospective randomized trials suggested that, over the range of solute clearance studies and using current standard PD technologies (mainly continuous ambulatory peritoneal dialysis (CAPD)), trying to achieve higher solute clearance goals had little clinical benefit for the population as a whole. Therefore, considerably more research is needed in the area of adequacy of PD. Additional randomized trials, optimally multicentered, to examine different PD doses are needed to

evaluate lower Kt/V urea in populations with larger patients with more comorbidity. A study that compares a group that maintains a peritoneal Kt/Vurea of 1.7 from the start of dialysis therapy (disregarding RKF) with a group that has a total Kt/Vurea of 1.7 (kidney plus peritoneal, which would require starting PD therapy with a minimal prescription with subsequent adjustment upward as RKF is lost) would be helpful. In addition, a randomized trial of different levels of small-molecule clearances is needed specifically for anuric patients on PD therapy. Trials with a longer follow-up than 2 years with assessment of nerve conduction to evaluate for neuropathy would be helpful. Markers of middle-molecule clearances also should be obtained long term. A randomized study to evaluate the influence of middle-molecule clearance or of full- versus partial-duration day dwells on patient outcomes would be valuable.

- Trials are needed in APD, with both dry day and wet days. A trial that compares outcomes with beginning PD on APD with a dry day versus beginning PD with a wet day (controlling for peritoneal dose), with the subsequent adjustment of the prescription (including the addition of a wet day), would be informative in evaluating the potential benefit of a dry abdomen for part of the day on protection of the peritoneal membrane and immune function. Such a study would need to include markers of the peritoneal membrane, as well as determination of middle molecules and neuropathy.
- Studies must be designed that separate the effects of volume control from those of small-molecule clearances. It is clear from the studies that have been done that volume overload sometimes is a consequence of using a limited number of exchanges in continuous ambulatory peritoneal dialysis (CAPD) and perhaps a consequence of excessively short nighttime exchanges in APD, in which the ultrafiltration volume is likely to be 50% sodium free.
- Because increasing small-molecule clearance does not appear to be the path to improved survival, studies investigating other maneuvers to decrease mortality should be investigated. Attention should be focused on specific causes of mortality. These studies could include use of an ACE inhibitor in combination with a lipid-lowering drug versus ACE inhibitor alone, monthly follow-up to assess and adjust the prescription to maximize volume status versus less frequent visits, and to evaluate cardiovascular deaths. Anuric patients are more likely to die a sudden death. Data from the same group indicate that hypokalemia is a risk factor for death; in this study, hypokalemia was defined by 3 measurements of potassium during 12 weeks, and sudden death was not more frequent in this group. Therefore, it seems possible that hypokalemia might be more common in anuric patients, possibly because of dietary and nutritional issues, and contribute to sudden death, but this needs to be studied.
- Another area that might prove fruitful to decrease morbidity and mortality is further research on decreasing the risk for, and managing, peritonitis. The risk for death related to peritonitis is variable from a low of 3% of deaths in Canada to 16.6% of deaths in Hong Kong. Aggressive catheter removal for refractory peritonitis versus delayed catheter removal (in an attempt to decrease mortality related to peritonitis) may result in a decrease in peritonitis-related deaths. Peritonitis remains the leading cause of technique failure and affects peritoneal function during the first year on PD therapy. Additional research on training methods and exit-site care may prove fruitful.
- Last, studies of maneuvers to improve adherence with the prescription and

diet are much needed in PD patients, especially in such countries as the United States, where adherence is less than optimal. Such maneuvers might include closer monitoring, treatment of depression, evaluation of supplies with home visits, etc.

- The presence of RKF was rather arbitrarily defined in this document by the Work Group as 100 mL of urine output per day. This was chosen because many of the studies on clearances chose 100 mL/d as the cutoff value. However, it is not clear that this is the most appropriate level of urine output to use, or even if urine volume, rather than measured GFR, would be preferable. Additional research is needed in this area.

Guideline 3: Preservation of Residual Kidney Function (RKF)

Research Recommendations

- Rigorous studies are needed to examine whether the use of radiocontrast dye affects RKF in dialysis patients and whether renoprotective strategies in the nondialysis population also apply to those on dialysis therapy. Although controversial, it was suggested that the rate of decrease in RKF in those on APD therapy compared with those on CAPD therapy is faster. More data are needed. Because of financial issues and ease of administration, use of aminoglycoside antibiotics for the treatment of peritonitis has been recommended. Therefore, data about whether long- or short-term use of aminoglycosides is associated with a more rapid decrease in RKF would be helpful. The USRDS analysis80 showed an association between use of ACE inhibitors and also use of calcium channel blockers with better preservation of RKF. Subsequent studies examined ACE inhibitors and ARBs, but not the use of calcium channel blockers; therefore, additional studies are needed. Clinical evaluation of the continuing use of immunosuppressive therapy (other than calcineurin inhibitors) to maintain residual kidney allograft function in patients on dialysis therapy is lacking. Also unclear is whether the benefit of attaining normotension by vigorous ultrafiltration is offset by the decrease in RKF from the attendant volume depletion.
- Data for the effect of peritonitis on RKF are contradictory. Studies examining the impact of peritonitis, as well as the treatment approach, on RKF are needed. In particular, the severity of peritonitis may relate to loss of RKF with more severe episodes (for example, fungal or those caused by gram-negative bacilli) perhaps more likely leading to loss of RKF.

CPR for Guideline 3

- Current guidelines recommend assessing peritoneal transport status by using peritoneal equilibration test (PET). They subsequently recommend a hypertonic dwell (4.25% dextrose) to work up a patient with ultrafiltration failure. Studies that compare 1.36%/1.5% dextrose or 2.27%/2.5% dextrose PET with 3.86%/4.25% dextrose PET are minimal. Because the 3.86%/4.25% test is recommended for the workup of ultrafiltration failure, more comparison data are needed. Furthermore, most kinetic modeling programs use data from 2.27%/2.5% dextrose PET to predict solute clearance and ultrafiltration. One needs to evaluate whether current kinetic modeling programs are as accurate if 4.25% PET is used; alternatively, if not, one may want to develop programs that use 4.25% dextrose PET data specifically.

Once done, the standard PET may be changed to a 4.25% dextrose PET.

Guideline 4: Maintenance of Euvolemia

Research Recommendations

- Randomized trials to determine optimal blood pressure targets for PD patients are required. Larger randomized trials looking at the effect of newer dialysis solutions on important patient outcomes also would be helpful. Studies looking at the relationship between peritoneal hypertonic glucose exposure and metabolic and cardiovascular outcomes, as well as patient survival, would be valuable.
- Euvolemia in home dialysis patients is not always readily achieved because patients may not be knowledgeable about this aspect of PD. A study examining training methods emphasizing evaluation of "euvolemia" as done by the patient on impact of blood pressure and volume status would be worthwhile. In addition, there are few, if any, studies of interventions to enhance patients' abilities to follow a rather rigorous diet in regard to sodium intake. Such studies should be undertaken.

Guideline 5: Quality Improvement Programs

Research Recommendations

- CQI programs were shown to improve specific outcomes for subgroups of patients, such as peritonitis rates, exit-site infection rates, technique failure rates, etc. It would be important to develop a better understanding about which factors also improve patient well-being and satisfaction with their modality. Current guidelines recommend assessing peritoneal transport status by using PET. They subsequently recommend a hypertonic dwell (4.25% dextrose) to work up a patient with ultrafiltration failure. Studies that compare 1.36%/1.5% dextrose or 2.27%/2.5% dextrose PET with 3.86%/4.25% dextrose PET are minimal. Because the 3.86%/4.25% test is recommended for the workup of ultrafiltration failure, more comparison data are needed. Furthermore, most kinetic modeling programs use data from 2.27%/2.5% dextrose PET to predict solute clearance and ultrafiltration. One needs to evaluate whether current kinetic modeling programs are as accurate if 4.25% PET is used; alternatively, if not, one may want to develop programs that use 4.25% dextrose PET data specifically. Once done, the standard PET may be changed to a 4.25% dextrose PET.
- Quality improvement programs are rather time consuming and therefore costly. A cost analysis of the impact of aggressive interventions by a program on outcomes should be carried out.

Guideline 6: Pediatric PD

Research Guidelines

- Pediatric data are sparse, in part because there are few clinical trials using RR for death as an outcome for adequacy. However, there are other important aspects of overall patient care that need to be considered and evaluated. These include the development of a simplified means to estimate glomerular rate in children that precludes the need for urine collection and that is accurate at low levels (stages 4 to 5 CKD) of kidney function, determination of adequate and optimal total solute clearance in children receiving PD, comparison of the impact of peritoneal solute clearance versus RKF on patient outcome, evaluation of PD and the longevity of dialysis therapy on QOL of pediatric patients and their families, determination of the ability of icodextrin-based dialysis solutions to enhance ultrafiltration across the age/size spectrum of pediatrics, and evaluation of the safety and efficacy of ACE-inhibitor, ARB, and diuretic therapy in children with CKD stage 5 receiving PD.

Guideline 1: Patient Preparation for Permanent HD Access

Research Recommendations

- Studies are required to determine the optimal vascular mapping criteria based on outcome goals of working fistulae.
- Studies are needed to determine the optimal stratification of patients for fistula placement. Is there an age component to sizing of the artery and vein for fistula creation? Specifically, should the minimal vein diameter for such higher risk groups as female, diabetic, and elderly patients be larger to have acceptable working fistula outcomes?
- Randomized studies should be performed comparing 1-stage with 2-stage brachial basilic vein transposition fistula outcomes.
- Studies are needed to determine the optimal surgical techniques for fistula creation with outcomes to identify factors that minimize the development of surgical swing segment stenosis in fistulae.

Guideline 2: Selection and Placement of HD Access

Research Recommendations

- **Patients should be considered for construction of a primary fistula after failure of every HD access.** There is a paucity of information about the success of this strategy. If a forearm loop AVG is placed as initial access, does this lead to successful construction of elbow-level fistulae? How often? Do we need an RCT? In what patients would a graft before fistula be cost- and resource effective? None? Some? Would a PU "immediate use" type of graft be preferable to a catheter if one had to do immediate (ie, within days) dialysis?
- How often is primary conversion of dysfunctional grafts to fistulae successful? Is it affected by the previous history of thrombosis or angioplasty (if applicable)? What are the guidelines for number of angioplasties/thrombectomies performed before compromising the ability to convert to a fistula? What is the optimal timing for conversion?
- **The preference for fistulae is based on lower morbidity associated with their creation and maintenance compared with other access types. Is this still true for the US CKD stage 5 population?**
- Has this remained true as the population has grown older and the health care system in the United States has been stretched? Late referrals, lower skill sets in the staff delivering dialysis and cannulating accesses, increased comorbidity in the United States compared with Europe, Japan, or Canada—do these factors influence the selection of initial access and the progression and choices among different access types?

Guideline 3: Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

Research Recommendations

- Can intensive structured cannulation training lead to better access outcomes?
- Can increased remuneration for expert cannulators lead to better access outcomes?
- Can self-cannulation lead to better outcomes?

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Research Recommendations

- Studies are needed to compare outcomes of physical examination with "high-tech" methods in determining the best timing for intervention.
- The role of DDU as an intermediate diagnostic test should be examined to determine the "timing" for access intervention with percutaneous transluminal angioplasty (PTA) or surgery.
- There may be important differences in the susceptibility of grafts and fistulae to thrombosis as a function of absolute access flow or change in access flow over time. The "best" therapy for the access also may differ according to type. Future studies should carefully separate the surveillance data, type of intervention (PTA or surgical), response to therapy, and both short-term and long-term outcomes according to access type, either graft or fistula. Because more proximal accesses have greater flow rates, data also should be categorized to access location, primarily the feeding artery (radial or ulnar versus low brachial, high brachial, and axillary for the upper arm and femoral for the thigh).
- Studies are needed to establish objective criteria for endovascular intervention.

Guideline 5. Treatment of Fistula Complications

Research Guidelines

- The efficacy of physical examination in detecting abnormalities in accesses difficult to cannulate should be studied.
- Comparative trials are required to assess interventional versus surgical modalities to correct maturation failure with measurement of access flow longitudinally before and after correction.
- Studies should examine the effect of intervention on: recurrent stenosis, elastic recoil, and juxta-anastomotic stenoses.

Guideline 6. Treatment of AVG Complications

Assessing adequacy of the intervention

- Is PTA an effective intervention for treatment of vascular access–related stenosis? We cannot answer this question. A fundamental problem is our inability to reliably predict the outcomes of our percutaneous and surgical interventions. The true determinants of HD graft patency and longevity remain unknown. It certainly is a complex and multifactorial process. The primary determinants of graft failure likely are regulated by both physiological and genetic factors and therefore are variable within the patient population. To add to the confusion, neointimal hyperplastic stenoses develop simultaneously and sequentially in multiple locations. Our success in treating 1 stenosis is negated by the rapid development of another lesion. And there is another important variable: delayed elastic recoil can cause rapid recurrence of the stenosis after an apparently successful angioplasty procedure. This phenomenon can occur minutes to hours after balloon dilation, and our anecdotal experience suggests that elastic recoil of a stenosis may happen after 10% to 15% of our angioplasty procedures. Our current challenge is to identify the determinants for successful angioplasty and optimize our techniques to improve our clinical outcomes. In addition, we need to develop pharmacological means to reduce/prevent the recurrence of neointimal hyperplasia after successful angioplasty.

Criteria for success

- An end point is used to define the successful completion of a procedure. The definition of a successful procedure can be viewed from several different perspectives. For example, the end point for clinical success is alleviation of the patient's symptoms. Hemodynamic success is restoration of normal blood flow throughout the treated vascular segment. And for treatment of stenoses, the end point for anatomic success is less than 30% residual diameter reduction. These clinical, hemodynamic, and anatomic end points serve as the determinants of a successful endovascular intervention. Our clinical experience has shown that these commonly used end points are unreliable for predicting the long-term patency of an HD graft or fistula. Although we use end points to define immediate success, there is no postprocedural end point that correlates with long-term patency. Our inability to predict the long-term outcome of our endovascular procedures continues to frustrate both the physician and patient.
- After an endovascular intervention, the standard definition of anatomic success is a residual stenosis with less than 30% diameter reduction. Although there are well-recognized physiological concepts that support the use of 50% stenosis as the definition of a hemodynamically significant lesion, there is no such scientific basis for the use of less than 30% residual stenosis to define a successful treatment. A consensus committee reached the value of 30% with representatives from interventional radiology and vascular surgery. This well-accepted standard end point (<30% residual stenosis) has no hemodynamic or physiological meaning. In addition, the residual stenosis does not allow for proper remodeling of the vein and may contribute to recurrence of stenosis. Therefore, it is not surprising that use of this parameter as a determinant of success is not predictive of the long-term

patency of an HD graft or fistula. This poor correlation between degree of residual stenosis and subsequent patency was substantiated in a study that reported analysis of 96 interventions performed in native AVFs.630 After angioplasty, 17 lesions had greater than 30% residual stenosis and, by definition, had failed treatment. However, there was no difference in the long-term patency of this group compared with patients who had lesions with less than 30% residual stenosis on final fistulography.

- Obviously, criteria used for success need to be examined by well-designed outcome studies.

Multiple lesions and criteria for intervention.

- According to the KDOQI guidelines, lesions with less than 50% stenosis should not be treated. However, it is not uncommon for a graft or fistula to have multiple areas of endoluminal irregularity that, when measured individually, represent less than 50% stenosis and therefore should not be treated. However, a hemodynamic abnormality may still exist. The basic principles of hemodynamics state that the effects of multiple stenoses are additive, similar to an electrical circuit with a series of multiple resistors. Therefore, our current concepts that emphasize the evaluation of individual stenoses using anatomic criteria are flawed.
- New methods[54] that provide a more global assessment of the entire vascular access circuit suggest that subtle lesions can have substantial hemodynamic effects. The assessment of intragraft blood flow during angioplasty procedures may provide additional information regarding the hemodynamic importance of lesions that are greater than 30% but less than 50% stenosis.
- We need to identify physiological/objective criteria for successful intervention.

I. ADULT GUIDELINES

Guideline 1: Use of Panels of Nutritional Measures

Research Recommendations

- Studies are needed to determine the most effective combination of measures of nutritional status for evaluating protein-energy malnutrition.

Guideline 2: Panels of Nutritional Measures for Maintenance Dialysis Patients

Research Recommendations

- Research is necessary to identify and validate the following:
    - The optimal panel of measures to screen for disorders in nutritional status.
    - The optimal panel of measures for a comprehensive assessment of nutritional status.
    - The optimal frequency with which these nutritional measures should be employed.
- More information is needed concerning the appropriate parameters to be used for assessment of body composition (eg, for expressing dual energy x-ray absorptiometry [DXA] measurements, anthropometry, and the creatinine index).
- Patient subgroups should be identified (eg, elderly, obese, severely malnourished, or physically very inactive individuals) for whom the use of specialized combinations of body composition measures are beneficial.

Guideline 3: Serum Albumin

Research Recommendations

- More information is needed concerning the relative contributions of nutritional intake and inflammatory processes to serum albumin concentrations.
- There is a need for a better understanding of the mechanisms by which hypoalbuminemia or the factors causing hypoalbuminemia lead to increased morbidity and mortality in dialysis patients.
- Studies are needed to assess whether and under what conditions nutritional intervention increases serum albumin concentrations in hypoalbuminemic dialysis patients.
- Will an increase in serum albumin levels induced by nutritional support reduce morbidity and mortality in persons undergoing dialysis?

Guideline 4: Serum Prealbumin

Research Recommendations

- What range of serum prealbumin concentrations is associated with optimal outcome?
- More information is needed concerning the relative contributions of nutritional intake and inflammatory processes to serum prealbumin levels.
- Data are needed concerning the mechanisms by which low serum levels of prealbumin lead to increased mortality in dialysis patients.
- Will nutritional intervention in malnourished hypoprealbuminemic dialysis patients increase serum prealbumin concentrations?
- Will an increase in serum prealbumin levels induced by nutritional support reduce morbidity and mortality in individuals undergoing dialysis?

Guideline 5: Serum Creatinine and the Creatinine Index

Research Recommendations

- The degree of correlation of the serum creatinine and creatinine index with skeletal muscle mass and dietary protein intake (DPI), and the sensitivity to change in these parameters of creatinine metabolism, need to be better defined.
- The relationship between the creatinine index and the edema-free lean body mass or skeletal muscle protein mass needs to be defined for ESRD patients.
- The rate of creatinine degradation in ESRD patients needs to be defined more precisely.
- The level of serum creatinine and the creatinine index associated with optimal nutritional status and lowest morbidity and mortality rates need to be defined.
- The relationships between other markers of protein-energy nutritional status (eg, serum albumin, prealbumin, or anthropometry) and serum creatinine or creatinine index are limited, somewhat contradictory, and need to be further examined.
- Whether nutritional interventions that increase serum creatinine or creatinine index will improve morbidity or mortality in malnourished dialysis patients should be tested.
- The effects of age, gender, race, and size of skeletal muscle mass on the relationship between the serum creatinine and the creatinine index on morbidity and mortality need to be examined.

Guideline 6: Serum Cholesterol

Research Recommendations

- What are the conditions under which serum cholesterol is a reliable marker of protein-energy nutrition? What can be done to increase the sensitivity and specificity of the serum cholesterol as an indicator of protein-energy nutritional status?
- The relationships between other markers of protein-energy nutritional status (eg, serum albumin or anthropometry) and serum cholesterol are limited, somewhat contradictory, and need to be better defined.
- How does nutritional intervention in malnourished dialysis patients affect their serum cholesterol concentrations?
- Recent data suggest that serum cholesterol exhibits a negative acute-phase response to inflammation.42 The relationship among serum cholesterol, nutritional status, and inflammation needs to be further investigated.
- Why does mortality increase when the serum cholesterol falls outside the 200 to 250 mg/dL range?
- More information is needed about the patterns of morbidity and mortality associated with abnormal serum cholesterol concentrations in dialysis patients. For example, in these individuals, is cardiovascular mortality directly related to the serum cholesterol level and are malnutrition and mortality from infection inversely related to the serum cholesterol level?
- Additional data investigating the relationships among serum cholesterol, protein-energy nutritional status, morbidity, and mortality are needed for persons undergoing PD.

Guideline 7: Dietary Interviews and Diaries

Research Recommendations

- Techniques to improve the reliability and precision of dietary interviews or diaries for MD patients are needed.
- Other less laborious and more reliable methods to estimate nutrient intake, particularly energy intake, are needed.
- Predictability of morbidity, mortality, or other clinical outcomes.

Guideline 8: Protein Equivalent of Total Nitrogen Appearance (PNA)

Research Recommendations

- There are still a number of technical problems with measuring PNA in individuals undergoing HD or peritoneal dialysis that engender errors and increase the costs of measurement. Research to decrease these sources of error would be useful.

- The mathematical relationship between PNA and protein intake in HD patients has not been well defined. A larger database to examine these relationships more precisely would be useful.
- More research into optimal methods for normalizing PNA to body mass would be valuable.

Guideline 9: Subjective Global Nutritional Assessment (SGA)

Research Recommendations

- The most effective technique for performing SGA needs to be identified. Is the currently recommended 4-item scale optimal? Should visceral proteins (eg, serum albumin, transferrin, and/or prealbumin) be added to the SGA? Should a standard reference of body mass be included (eg, BMI or % standard body weight (SBW))?
- The technique of SGA needs greater validation with regard to sensitivity, specificity, accuracy, intraobserver and interobserver variability, correlation with other nutritional measures, and predictability of morbidity, mortality, or other clinical outcomes.

Guideline 10: Anthropometry

Research Recommendations

- Age-, sex-, and race- or ethnic-specific desirable reference values for anthropometry obtained in large numbers of dialysis patients are needed.
- The risk of morbidity and mortality associated with different anthropometric measurements in dialysis patients should be determined.
- To determine whether anthropometry might be an acceptable intermediate outcome in nutrition intervention trials.
- Will improvement in anthropometric values through nutritional intervention be associated with decreased morbidity and mortality and enhanced quality of life in individuals undergoing dialysis?

Guideline 11: Dual Energy X-Ray Absorptiometry (DXA)

Research Recommendations

- The sensitivity and specificity of DXA as a marker of protein-energy nutritional status, and specifically body composition, need to be defined more precisely.
- Careful studies of the relationships between changes in more traditional markers of protein-energy nutritional status (eg, albumin, prealbumin, or anthropometry) and changes in body composition by DXA are needed.
- Whether DXA assessment of body composition might be an acceptable intermediate outcome in nutrition intervention trials needs to be determined.
- Whether DXA measurements correlate with morbidity and mortality in dialysis patients needs to be determined.

Guideline 12: Adjusted Edema-Free Body Weight (aBW_{ef})

Research Recommendations

- The use of the aBWef for assessment and prescription of nutritional intake must be validated.
- More precise and practical methods are needed for assessing the size of body water compartments and, in particular, undesirable increases or reductions in total body water, intracellular water, or extracellular or intravascular water.

Guideline 14: Treatment of Low Serum Bicarbonate

Research Recommendations

- The optimum serum bicarbonate and blood pH levels for dialysis patients need to be defined. There are data from individuals without renal insufficiency indicating that mid-normal or high normal blood pH range maintains better nutritional status than does the low-normal range.
- More research is needed on the long-term effects of correcting acidemia on clinical outcomes and particularly on intermediate nutrition-related outcomes as well as morbidity and mortality.
- The effect of correction of acidemia on muscle function and on beta-2 microglobulin metabolism needs more investigation.

Guideline 15: Dietary Protein Intake (DPI) in Maintenance Hemodialysis (MHD)

Research Recommendations

- More studies are needed on the relationship between the quantity and type of DPI and nutritional status, morbidity, mortality, and quality of life in HD patients. Long-term, randomized, prospective clinical trials would be particularly helpful in addressing these questions. To reduce the large costs for such studies, innovative investigational tools are needed.
- Information concerning dietary protein requirements of special subsets of HD patients is needed. Such subsets include individuals with protein-energy malnutrition (PEM) or low dietary energy intake (DEI), obese individuals, and the elderly.

Guideline 16: Dietary Protein Intake (DPI) for Chronic Peritoneal Dialysis (CPD)

Research Recommendations

- The Research Recommendations for management of dietary protein intake (DPI) for patients treated with maintenance peritoneal dialysis are similar to those for patients treated with HD.

- Studies to determine the optimum protein intake should be undertaken in subsets of PD patients, including those who are elderly, malnourished, obese, or who have a low energy intake or catabolic illness such as peritonitis.

Guideline 17: Daily Energy Intake for Maintenance Dialysis Patients

Research Recommendations

- Few studies have examined energy requirements of persons undergoing HD or PD. Hence, there is a great need for more research in this area. It would be of particular value to conduct both carefully controlled metabolic studies, as well as long-term, randomized outpatient clinical trials, particularly in which patients are randomly assigned to different energy intakes. It would be helpful to relate daily energy intake to morbidity, mortality, and quality of life scales, as well as to nutritional measures. To reduce the high cost and length of time to collect such data, innovative investigative tools to address these issues are needed.
- Studies are needed to assess the optimal energy requirements of subsets of dialysis patients (eg, individuals with protein-energy malnutrition (PEM), patients with superimposed catabolic illnesses, obese individuals, and elderly patients).
- Studies are needed to examine whether increasing energy intake of dialysis patients with protein or energy malnutrition would be beneficial to the patients.
- Assessment of energy intake is laborious, time-consuming, and therefore expensive. Developmental studies to create accurate and less costly methods for assessing energy intake are greatly needed.

Guideline 18: Intensive Nutritional Counseling With Maintenance Dialysis (MD)

Research Recommendations

- A better understanding of the effects of nutrition intervention counseling methods (including quality of life scales) on nutritional intake, nutritional status, morbidity, and mortality should be evaluated in dialysis patients.

Guideline 19: Indications for Nutritional Support

Research Recommendations

- Conduct a randomized clinical trial comparing oral nutritional supplements, tube feeding, and intradialytic parenteral nutrition (IDPN) in malnourished dialysis patients. Outcomes should include survival, morbidity, and quality of life as well as nutritional status.
- Research is needed to define the optimal composition of oral supplements, enteral nutrition, and intradialytic parenteral nutrition (IDPN) formulas for dialysis patients.
- Conduct studies of the indications for nutritional support in dialysis patients.

- Determine the optimal timing for intraperitoneal amino acids (IPAA) administration (eg, daytime CAPD versus nighttime with cycler).
- Evaluate the effects of IPAA on physical function, hospitalization, and other clinical outcomes.
- Examine the clinical value and cost-effectiveness of nutritional support through hemodialysate.

Guideline 21: Energy Intake During Acute Illness

Research Recommendations

- Studies to define the optimal protein intake for the dialysis patients who are acutely ill are needed.
- The effects of different levels of protein intake on patient outcome and on nutritional markers are needed. Because increasing protein intake may alter dialysis requirements, the effect of higher levels of protein intake on the optimal dose of dialysis should be defined.
- The energy needs of acutely ill dialysis patients should be better defined. It would be particularly valuable to define how energy needs may vary with different protein and amino acid intakes.
- The development of simple and inexpensive methods for determining the energy expenditure in individual acutely ill patients would be very helpful.
- The optimal mixes of energy sources (ie, protein, amino acids, carbohydrates, and fat) for acutely ill dialysis patients should be defined.
- Studies are needed that examine which energy intakes are associated with the most optimal clinical outcomes.

Guideline 22: L-Carnitine for Maintenance Dialysis Patients

Research Recommendations

- Additional clinical trials in the area of erythropoietin-resistant anemia, carefully accounting for anticipated differences in response based on factors such as iron stores and the level of inflammatory mediators.
- Further definition of the L-carnitine response by taking an "outcomes" approach to patients treated with L-carnitine. Can patient subgroups be identified who are likely to respond to L-carnitine for one or more of its proposed indications? Are certain individuals uniform "responders" across indications (a "carnitine-deficient" phenotype) or do certain patient characteristics predict specific responses?
- A randomized clinical trial of L-carnitine in dialysis patients with cardiomyopathy and reduced ejection fraction.
- A randomized clinical trial of L-carnitine for the treatment of hyperlipidemia, restricted to patients with preexisting hyperlipidemia.

The constant used in this last equation (0.029 kg/mg/24 h) was derived from individuals without renal disease234 and should be reevaluated for ESRD patients; at least one study suggests that this constant is also applicable for dialysis patients. Skeletal or cardiac muscle protein intake as well as total protein intake can affect the creatinine index,235,236 and marked variations in these nutrients may therefore have major effects on the creatinine index. Thus, until the

relationships between total protein intake and muscle intake and the creatinine index are well defined for ESRD patients, some caution must be exercised in interpreting the creatinine index, particularly if the diet of the individual in question is particularly high or low in these nutrients.

Guideline 23: Panels of Nutritional Measures for Nondialyzed Patients

Research Recommendations

- More sensitive and specific measures of protein-energy nutritional status in CKD/kidney failure patients need to be developed.
- Studies are needed to test whether monitoring nutritional status in individuals with progressive CKD/kidney failure by a combination of measures is beneficial for detecting and preventing malnutrition.
- Additional research is needed to define more accurately the combination of measures that provides the most useful information concerning the nutritional status of individuals with CKD/kidney failure.

Guideline 24: Dietary Protein Intake for Non-Dialyzed Patients

Research Recommendations

- Which subpopulations of patients with progressive chronic renal disease are particularly likely or unlikely to display slowing in the decline of their GFR with dietary protein restriction?
- Are there any additive benefits to prescribing both low protein diets and angiotensin converting enzyme inhibitors for patients with progressive chronic renal disease?

Guideline 25: Dietary Energy Intake (DEI) for Non-Dialyzed Patients

Research Recommendations

- Studies are needed to assess why spontaneous DEI is reduced in persons with kidney failure who are not undergoing dialysis.
- More data are needed on the energy requirements of clinically stable patients with CKD. There are very few data in this area.
- Data are also needed on the energy requirements of individuals with kidney failure who are obese or malnourished or who have associated catabolic illnesses.
- What techniques can be used to increase energy intake in individuals with CKD and kidney failure?

Guideline 26: Intensive Nutritional Counseling for Chronic Renal Failure (CRF)

Research Recommendations

- Why do apparently clinically stable patients with creatinine clearances under 50 mL/min often have decreased dietary protein and energy intakes and evidence of deteriorating nutritional status?
- What interventions are likely to prevent or reverse the developing PEM in these individuals?
- Will interventions that improve nutritional status reduce morbidity and mortality in these individuals?

Guideline 27: Indications for Renal Replacement Therapy

Research Recommendations

- Studies to assess the optimal timing and indications for commencing renal replacement therapy are needed.
- Serial evaluations of nutritional status in the course of these studies will help to determine whether initiation of dialysis indeed improves nutritional status.
- Studies should be conducted to determine whether any GFR level can be used to indicate when maintenance dialysis should be initiated.
- Whether earlier initiation of renal replacement therapy can prevent the development or worsening of PEM and its attendant complications needs to be evaluated in a controlled study.

II. PEDIATRIC GUIDELINES

Guideline 1: Patient Evaluation of Protein-Energy Nutritional Status

Research Recommendations

Investigation in the following areas to standardize interpretation in children with renal disease:

- PNA
- Subjective Global Assessment (SGA) for pediatric patients
- Prealbumin.

Guideline 2: Management of Acid-Base Status

Research Recommendations

- Studies are needed to delineate the role of acidosis on growth retardation in the setting of ESRD in children.

- Whether or not correction of acidosis may improve the poor response to recombinant human GH in pediatric patients treated with dialysis needs to be elucidated.

Guideline 3: Urea Kinetic Modeling

Research Recommendations

- Appropriate correlations between calculated and measured data need to be established. The impact of the PNA on growth needs to be better defined, and the need to normalize the data to some measure of body size must be assessed. Longitudinal data of PNA, along with dietary protein and energy intake, must be collected and correlated against accepted parameters of growth and nutritional status.
- There is a need for the development of a validated formula to calculate V in children treated with peritoneal dialysis. The reported studies described above calculated the urea volume of distribution based on formulas developed in normal children. It is not clear whether children with renal failure and on peritoneal dialysis are characterized by the same formula.
- Assess the ability of a kinetic model of solute removal for children treated with CAPD and automated peritoneal dialysis to accurately reflect the nutritional status of these patients and establish a valid model for children treated with all forms of peritoneal dialysis. The relationship between weekly creatinine clearance and weekly Kt/V for children treated with CAPD is not the same as that for children treated with automated peritoneal dialysis. Correlations may differ between modalities.

Guideline 4: Interval Measurements

Research Recommendations

- The use of bioelectrical impedance (BIA) and DXA technologies to measure body composition should be explored.
- The measurement of IGF-I or IGF-binding protein levels to reflect nutritional adequacy should be explored.
- The value of using a selective dietary interview/diary and the use of nPNA to assess DPI should be determined.

Guideline 5: Energy Intake for Children Treated With Maintenance Dialysis

Research Recommendations

- Given the lack of specificity of the recommended dietary allowance (RDA) for calories, and the fact that the RDA was devised to apply to a population of normal children, clearer data on the actual energy expenditure of children treated with dialysis are necessary. Indirect calorimetry can be utilized and resting energy and basal energy expenditure can be measured and compared with the RDA. The impact of the dialysis process on the children's energy expenditure should be assessed in this patient population. The availability of such information would allow a more appropriate initial diet prescription for

such patients.
- Prospective interventional trials should be designed to better understand the impact of various energy intakes on growth and nutritional status.

Guideline 6: Protein Intake for Children Treated With Maintenance Dialysis

Research Recommendations

- What is the optimal DPI for a child on HD or peritoneal dialysis?
- What is the optimal ratio of protein to non-protein calories?
- How can the impact of interventions on protein intake best be monitored?

Guideline 7: Vitamin and Mineral Requirements

Research Recommendations

- The vitamin and mineral needs of children undergoing dialysis should be determined by prospective, longitudinal studies conducted in patients not yet receiving vitamin and mineral supplementation.

Guideline 8: Nutrition Management

Research Recommendations

- Would adaptation of an SGA tool specifically for the pediatric population be useful for evaluating nutrition status of children?
- Studies are needed to evaluate strategies to enhance compliance, with particular emphasis on the adolescent age group.

Guideline 9: Nutritional Supplementation for Children Treated With Maintenance Dialysis

Research Recommendations

- The use of amino acid-based peritoneal dialysis solutions is potentially an attractive means of nutrition support. Studies should be conducted to determine the optimal dialysate amino acid profile and whether the amino acids should be combined with dextrose for better utilization of the protein source. Even with the addition of both dextrose and amino acids to dialysate, the total tolerable osmolality of the dialysate solution prevents the solutions from providing much energy. Thus, the solutions are more effective at providing an adequate amino acid or protein load than a sufficient energy intake.
- The impact of this therapy on the nutrient intake of patients, solute clearance, and patient growth when used on a long-term basis also requires further study.

Guideline 10: Recommendations for the Use of Recombinant Human Growth

Research Recommendations

- Studies are needed to better define the response to recombinant hGH in patients treated with dialysis, and whether higher doses of recombinant hGH would have a beneficial effect on linear growth remains to be established.
- Although it is recognized that control of secondary hyperparathyroidism is important prior to the initiation of therapy with recombinant hGH, serum PTH levels increase during therapy with recombinant hGH despite treatment with calcitriol. Thus, further studies should define the appropriate serum PTH levels that correspond to indices of bone remodeling during therapy with calcitriol and recombinant hGH in children treated with maintenance dialysis.

Guideline 1. Screening and Diagnosis of Diabetic Kidney Disease

Research Recommendations

What is the best screening test for DKD? Microalbuminuria is the best available test for screening of DKD, but it is imprecise. For this reason, additional research on the use of new biomarkers or better use of already available markers may lead to the important advances in this field. Markers may include:

- Urinary immunonreactive intact albumin and shed podocytes;
- Genetic risk indicators;
- Blood and/or urine changes in growth factors, cytokines, inflammatory markers, or markers of oxidative stress;
- Innovative kidney imaging or tissue studies.
- Appropriately weighted risk algorithms should be derived using predictive variables:
- AER within the normoalbuminuric or microalbuminuric range;
- Retinopathy status;
- Clinical and ambulatory blood pressure measurements;
- Glycemic control;
- Diabetes duration;
- Lipid levels;
- Age;
- Sex;
- Race;
- Family history.

Improved measures of glomerular filtration rate (GFR) should be developed and may include:

- More reliable creatinine measurement methods;
- Modifications of existing formulas;
- Application of new GFR markers, such as cystatin C;
- Development of simplified direct GFR measurements.

How should albuminuria be measured?
Additional studies on urinary albumin measurements, including predictive values of gender-specific ACR cutoffs, urine collection methods, and processing of urine samples, are warranted.
What is the rate of progression of DKD in people with reduced GFR, but normal urinary albumin excretion? How does this compare with the rate in those with elevated urinary albumin excretion?

- Does regression of albuminuria modify the long-term progression of DKD?

- What is the effect of promising agents to prevent RCN in patients with

various stages of CKD and both types of diabetes?
- What is the best common definition of RCN?

Guideline 2. Management of Hyperglycemia and General Diabetes Care in CKD

Research Recommendations

- Does intensive treatment of glycemia reduce progression of CKD, or prevent CKD stage 5 and CVD events, in people with diabetes and CKD (secondary prevention)? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?
- Do the TZDs have kidney or CVD benefits beyond glycemic control in people with diabetes and CKD?
- Are risks of fluid retention with TZDs greater in people with CKD?
- What is/are the best methods for assessing glycemic control in CKD?
- What are the best methods for administering insulin in patients on dialysis?
- What are the best ways of countering the hyperglycemic effects of glucocorticoids, cyclosporine, and tacrolimus in the transplant patient?
- Are there kidney or CVD benefits beyond glycemic control of GLP-1 analogues (incretin mimetic or amylin analog) or DPP-4 inhibitors in people with DKD?
- What are the risks in using GLP-1 analogues (incretin mimetic or amylin analog) or DPP-4 inhibitors in people with diabetes and CKD?

Guideline 3. Management of Hypertension in Diabetes and CKD

Research Recommendations

- What are optimal doses of ACE inhibitors and ARBs for kidney disease protection in people with diabetes and hypertension?
- What is the role of ARBs or other classes of antihypertensive agents, either alone or in combination with ACE inhibitors, on slowing kidney disease progression and preventing CVD in hypertensive people with DKD?
- What is the optimal level of blood pressure to slow DKD progression? The question regarding the optimal level of blood pressure reduction for cardiovascular risk reduction may be answered in 2008 by the ACCORD trial. However, this may not answer the question about kidney protection.
- Do ACE inhibitors or ARBs prevent progression of kidney disease in patients with diabetes and CKD, defined by low GFR without albuminuria?

Guideline 4. Management of Dyslipidemia in Diabetes and CKD

Research Recommendations

- What is the effect of lipid lowering with statins on CVD in patients with diabetes and CKD stages 1 to 4?
- What is the impact of inflammation (ie, high C-reactive protein) on the response to lipid lowering with statins in diabetes and CKD stage 5? This

question may be answered by subgroup analysis and biomarker determinations of the 4D participants.

- What is the effect of statin treatment on progression of DKD? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?

Guideline 5. Nutritional Management in Diabetes and CKD

Research Recommendations

- Randomized clinical trials in diabetes and CKD examining the role of nutrition on clinical outcomes are needed. Diet interventions are extremely challenging, but are required to identify new therapeutic options.
- Studies examining specific nutrients on kidney disease would be beneficial**.** What is the effect of 0.8 g of protein/kg body weight per day on GFR and urinary albumin excretion with the diet defined as follows:
    - 30% fat: 5% saturated, 5% omega-6, 10% omega-3, 10% omega-9.
    - 60% carbohydrate calories; predominantly (40% to 45%) whole grains, fruits, and vegetables.
- The above question modified for amino acid composition by altering the protein source:
    - soy protein;
    - lean poultry and fish;
    - vegetable protein only;
    - 50% protein as fish rich in omega-3 fatty acids.
- What is the best strategy for nutrition interventions? Evaluate types and frequency of nutrition education sessions provided by a registered dietitian in conjunction with medical management.
- What is the effect of nutritional intervention on progression of DKD using the diagnostic criteria defined in the NKF-KDOQI™ guidelines? Do effects differ by albuminuria status (normoalbuminuria, microalbuminuria, macroalbuminuria) or level of GFR?

CPR 1. Management of Albuminuria in Normotensive Patients With Diabetes and Albuminuria as a Surrogate Marker in DKD

Research Recommendations

- What is the effect of RAS inhibition (ACE inhibitors and ARBs) on albuminuria and clinical outcomes in normotensive people with DKD?
- What is the relationship between magnitude of albuminuria change and risks of CKD and CVD in people with DKD?
- What is the optimal “target value” for urine albumin excretion in DKD during treatment with ACE inhibitors and ARBs?
- Do different types of treatment that reduce albuminuria improve clinical outcomes in DKD?

CPR 2. Multifaceted Intervention for People With Diabetes and CKD

Research Recommendations

- Which facets of the intensive multifaceted intervention are associated with reduced risks of CKD and CVD?
- Do people with diabetes and CKD already treated with RAS inhibitors benefit from intensive multifaceted intervention?
- Does intensive multifaceted intervention provide CKD and CVD benefits at earlier or later stages of CKD in diabetes?
- Can intensive multifaceted intervention for diabetes and CKD be accomplished in other clinical settings?
- In overweight and obese people (BMI > 24.9 kg/m2) with diabetes and CKD, what is the effect of weight loss using a balanced calorie-restricted diet on glycemic control, GFR, urinary albumin excretion, and CVD risk factors?
- What are the benefits and risks of using rimonabant for weight loss in people with diabetes and CKD?

CPR 3. Diabetes and CKD in Special Populations

Research Recommendations

- What are the most effective means of translating clinical knowledge into public health interventions for DKD? While evaluation of direct clinical and public health efforts will be essential, development of systems models can be useful planning tools for predicting the most cost-effective way to use the limited resources that will be available in the countries most affected by DKD in the future.
- What are the prenatal and early childhood factors that lead to later development of diabetes and CKD?
- What are the causes of different risks of DKD progression and mortality after onset of kidney replacement therapy in various ethnic groups? Native Americans on dialysis therapy have better survival compared with Caucasians in the United States, while Canadian First Nations members have similar survival as Canadian Caucasians. This difference in relative survival suggests that nongenetic factors may play a significant role in survival.
- Are inexpensive combination antihypertensive agents safe and effective for DKD in populations of developing countries? Such an approach could have great clinical impact, particularly where limited resources are available for purchasing drugs. The effectiveness of low-cost interventions using less expensive generic drugs to control risk factors for DKD has been demonstrated in rural India.
- Are programmatic efforts to improve the care of patients with CKD worldwide effective, such as the NKF Kidney Disease—Improving Global Outcomes and the International Society of Nephrology Commission for the Global Advancement of Nephrology? These programs should be regularly assessed.
- What are effects of interventions that may decrease the risk of preeclampsia and preterm delivery in women with diabetes and CKD? This is an especially challenging population that should be included in clinical trials.
- What factors influence maternal and fetal outcomes in women with type 2

diabetes and CKD?

CPR 4. Behavioral Self-Management in Diabetes and CKD

Research Recommendations

- To what extent do low-dose combinations of medicines for treatment of diabetes and CKD reduce adverse effects and improve adherence?
- Do optimal interventions combine behavioral approaches with pharmacological therapies to improve management of risk factors for diabetes and CKD*?* Particular attention should be paid to identifying which behavioral strategies are most effective in producing the desired change.
- What are effective strategies for maintaining long-term adherence to self-care requirements for management of diabetes and CKD?

New Treatments for DKD

The Work Group recognizes the importance of bringing new treatments into clinical research for DKD, especially for patients who have progressive kidney disease despite the current standard of care. Promising treatments, including novel agents and potential new uses of existing agents, are currently in phase 2/3 trials for DKD (listed below).

Novel therapies:

- Protein kinase *C-β* inhibition—ruboxistaurin;
- Glycosaminoglycans—sulodexide;
- Inhibition of advanced glycation end product formation—pyridoxamine;
- Antifibrotic treatment—pirfenidone, anticonnective tissue growth factor antibody;
- Endothelin antagonism—avosentan, SP301;
- Direct renin inhibition—aliskiren.
- New uses of existing agents:
- Aldosterone blockade—spironolactone, epleronone;
- Anti-inflammatory—pentoxifylline;
- Peroxisome proliferator activators (TZDs)—rosiglitazone, pioglitazon.

KDIGO (Kidney Disease: Improving Global Outcomes) formed a work group for the management of dyslipidemia in patients with CKD. This work group developed a guideline that contains substantial changes from the 2003 KDOQI guideline on the same topic. To assist US practitioners in interpreting and applying the KDIGO guideline, NKF-KDOQI convened a work group to write a commentary on this guideline. For the most part, our work group agreed with the recommendations of the KDIGO guideline, although we describe several areas in which we believe the guideline statements are either too strong or need to be more nuanced, areas of uncertainty and inconsistency, as well as additional research recommendations. These research recommendations, in addition to those from the KDIGO guideline, are presented here.

KDIGO Research Recommendations

Chapter 1

- Assess the clinical effectiveness and economic merits of interventions to improve adherence to these recommendations, particularly those which are level 1. This includes better understanding of physician and patient barriers to guideline adoption and the contribution of polypharmacy.
- Examine secular trends in adherence to recommendations in this clinical practice guideline (CPG) and any secular changes in patient outcomes.
- Confirm real practice safety of statin use (outside of restrictive eligibility criteria used in RCTs). Specifically the frequency and severity of clinically relevant statin drug interactions should be studied in this population to improve the safety of statin prescribing.
- Assess the cost implications of less frequent or avoidance of cholesterol measurements, and confirm that less frequent measurements do not adversely affect the clinical benefits of treatment (compared to more frequent measurements).

Chapter 2

- An extended observational study should be undertaken of the SHARP study cohort to determine whether the reduction in major atherosclerotic events resulting from 5 years of LDL-C lowering persists in the long-term, and whether LDL-C lowering significantly delays renal disease progression in people with non-dialysis-dependent CKD
  and eGFR o60 ml/min/1.73 m2
- Given that the majority of early CKD is managed in primary care, audits of pharmacological cholesterol lowering treatment should be undertaken in this setting.
- Data from the AURORA, 4D and SHARP studies (dialysis cohort) should be pooled to undertake individual patient data meta-analysis to more comprehensively assess the benefits and risks of cholesterol-lowering treatment in people with dialysis-dependent CKD.

Chapter 3

- Future studies should be conducted to determine the prevalence of dyslipidemias among children initiating dialysis or receiving a kidney transplant.

Chapter 4

- Future studies should be conducted to assess short- and longterm association between lipids and CVD, using surrogate outcomes such as carotid intima-media thickness and clinically relevant outcomes such as MI and stroke.

Chapter 5

- There are currently no published randomized trials of fibric acid derivatives in CKD populations and too few participants with CKD were included in previous trials to provide reliable information. Other agents, such as niacin and the cholesteryl ester transfer protein inhibitor anacetrapib are currently being investigated in clinical trials in the general population and deserve investigation in CKD patients.
- CKD registries should report hypertriglyceridemia-induced pancreatitis to identify true incidence.
- Studies should be conducted to confirm that pancreatitis due to TG levels above 11.3 mmol/l (1000 mg/dl) is infrequent in HD patients.

Chapter 6

- Determine prevalence of hypertriglyceridemia in pediatric kidney transplant recipients.
- Determine the effect of diet and weight loss in lowering TG among pediatric CKD patients.

Additional KDOQI Research Recommendations

Adults

- Evaluate accuracy of current risk calculators for CVD in CKD
- Evaluate whether calculators should incorporate albuminuria, estimated GFR, or both
- Develop CVD risk calculators for individuals aged 18-40 y with CKD
- Evaluate the utility of measuring lipoprotein(a), apolipoprotein B, and other markers of dyslipidemia in CKD
- Evaluate the degree to which low adherence prevents the expected reduction in LDL cholesterol associated with statin initiation among individuals with CKD
- Assess LDL cholesterol response to statins among patients with CKD
- Evaluate whether follow-up lipid measurements provide useful information
- Evaluate whether duration of disease, particularly pediatric onset, should be overtly considered in risk assessment and lipid treatment guidelines
- Randomized trials of fibrates in patients with CKD to clarify the benefits and risks of fibrates in this population
- Studies assessing the incidence of hypertriglyceridemia-induced pancreatitis and the burden of pancreatitis due to triglycerides > 1,000 mg/dL among both hemodialysis and peritoneal dialysis patients

- Observational studies and randomized trials of lipid treatment in peritoneal dialysis patients
- Randomized controlled trial of statin vs no statin in a representative US kidney transplant recipient population with primary end point of cardiovascular mortality and secondary end points of major adverse cardiovascular event, administered from time of transplantation
- Randomized controlled study of statin vs no statin in a representative US kidney transplant recipient population, stratified by level of cardiovascular risk factors, with primary end point of cardiovascular mortality and secondary end points of major adverse cardiovascular event, administered from time of transplantation

Pediatric

- Determine the association between lipids in childhood CKD with development of CVD many years later
- Develop risk calculators for CVD in pediatric CKD
- Obtain short-term primary pharmacokinetic/dynamic and drug safety data in children with reduced GFR, those with significant proteinuria, and those with kidney transplants
- Develop and validate surrogate outcomes for CVD in the pediatric population
- Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein.

Recommendation 1: Evaluation of Growth and Nutritional Status

Research Recommendations

- Validity of 3-day diet records and 24-hour recalls in the CKD population in whom underreporting of restricted foods may be common.
- Identification of clinically relevant biomarkers for—and clinical predictors of—CKD related protein-energy wasting.
- Determination of the prevalence of protein-energy wasting in pediatric CKD and how this relates to severity of CKD.
- Predictive value of BMI SDS in identifying protein-energy wasting.
- Identification of simple clinical markers of protein-energy wasting.
- Identification of objective methods of determining volume status.
- Further study of nPCR is warranted to identify nPCR values reflecting adequate protein intake for different pediatric patient age groups.
- The normalized PNA (nPNA) should be studied as an objective measure of protein intake for children receiving maintenance PD.
- Further work to develop and validate multiparameter nutritional assessment scales, such as the SGA, is warranted.

Recommendation 2: Growth

Research Recommendations

- Evaluations of rhGH dosing regimens that are titrated to the level of IGF-1.
- Study of non–growth-related benefits of rhGH therapy in children, such as psychosocial and quality-of-life benefits, bone development, neurodevelopment, and cardiovascular benefits.
- Evaluation of methods to overcome the poor use of rhGH in children with CKD and poor growth.
- Study of the pathophysiological factors contributing to poorer response to rhGH in children on dialysis therapy compared with children before dialysis therapy.
- Further study of the impact of frequent HD on growth, with or without the use of rhGH.
- Studies of the effect of CKD-related acidosis and its treatment will need to assess children who are acidotic at baseline because it would be unethical to randomly assign children to an acidosis arm prospectively. The clinical and animal model data cited argue for correction of or controlling for the presence of acidosis in any study assessing growth outcomes in pediatric patients with CKD. Recent preliminary data for more frequent or intensive HD demonstrate improved growth profiles that could be explained in part by improved acid-base status. Such studies should be expanded in the future.

Recommendation 3: Nutritional Management and Counseling

Research Recommendations

- The effect of intensive and frequent dietary counseling for nutritional intake, nutritional status, quality of life, and occurrence of nutrition-related morbidities should be evaluated at various stages of CKD to identify how early in the progression of CKD nutrition intervention should occur and aid in determining adequate allocation of pediatric renal dietitians within programs.
- Studies are needed to evaluate strategies to enhance dietary adherence, with particular emphasis on the adolescent age group.

Recommendation 4: Energy Requirements and Therapy

Research Recommendations

- Determination of energy requirements at different stages of CKD and with different methods of kidney replacement therapy.
- The role of enteral feeding in the older child and adolescent in preventing the development of protein-energy wasting syndrome.
- Research should be directed to further delineation of the role and dose of IDPN to treat and/or prevent malnutrition in specific pediatric HD populations, including those receiving more frequent HD.
- Research should be conducted to evaluate the tolerance of pediatric HD patients to intradialytic oral nutritional supplementation. The quantitative contribution of the
- Research should be conducted to better delineate:
- the risks and benefits of treatments such as n-3 FA/fish-oil supplementation and plant stanols in children with CKD and dyslipidemia.
- the impact of dietary and lifestyle factors on managing overweight/obesity in children with CKD and whether weight management has an impact on progression of kidney disease, morbidity, and mortality.

Recommendation 5: Protein Requirements and Therapy

Research Recommendations

- Controlled prospective studies are required to compare the long-term effects of different levels of DPI on growth, nutritional status, serum phosphorus levels, and cardiovascular morphology and function in children with CKD stages 2 to 5 and on dialysis therapy.
- Phosphorus bioavailability studies in humans for various dietary protein sources are needed to provide comprehensive evidence-based identification of preferred dietary protein sources.
- In children on PD therapy, amino acid–containing dialysis solutions are

available that permit the provision of nitrogen carriers without any phosphate load. Whereas the use of 1 bag of amino acid fluid per day did not consistently improve the nutritional status of children on CAPD therapy, recent short-term studies have suggested an anabolizing effect of combined peritoneal administration of glucose and amino acids in children and adults on automated PD (APD) therapy. This concept requires further exploration in long-term randomized clinical trials. Longitudinal growth and nutritional status, as well as indicators of PD efficacy and safety, should be studied.

Recommendation 6: Vitamin and Trace Element Requirements and Therapy

Research Recommendations

- Assess the selenium status of children with CKD stages 2 to 5 and 5D.
- Assess the vitamin and trace element needs of children with CKD and those on dialysis therapy by studying dietary intake and blood levels of these patients before and after supplementation.
- Assess the vitamin and trace element needs of patients receiving frequent HD.
- Further the development of a vitamin and trace element formulation designed to specifically meet the needs of pediatric patients.

Recommendation 7: Bone Mineral and Vitamin D Requirements and Therapy

Research Recommendations

- Short-term calcium balance studies and controlled long-term outcome studies are required in children receiving HD and PD to determine the relative roles of dietary calcium, calciumcontaining phosphate binders, and dialysate calcium in the development of hypercalcemia, extraskeletal calcifications, CVD, adynamic bone disease, and bone fractures.
- Calcium balance between children with CKD with and without oligoanuria should be compared.
- The long-term safety of non–calcium-containing phosphate binders in infants and young children requires further investigation.
- The dose-response relationship, as well as the comparative safety and efficacy, of different administration intervals (daily versus monthly) of equivalent total doses of ergocalciferol or cholecalciferol should be studied across pediatric age groups.
- The effects of ergocalciferol and cholecalciferol supplementation on serum 1,25(OH)2D, PTH, calcium, and phosphorus levels and bone and cardiovascular end points should be studied in prospective controlled trials in children with different stages of CKD, including dialysis.
- The impact of various 25(OH)D treatment regimens on bone health of children with CKD.

- Randomized clinical trials are needed to assess the long-term impact of dietary phosphorus restriction on biochemical parameters, bone mineral density, linear growth, nutritional status, preservation of kidney function, and cardiovascular function in children across the age groups with CKD stages 2 to 4.
- Studies are needed to evaluate whether lowering serum phosphorus levels into the normal or low-normal range improves clinical outcomes in children with CKD stages 4 to 5 and 5D, including assessments of coronary artery calcification, intima-media thickness of large arteries, and arterial elasticity indices.
- Prospective comparative studies are needed to evaluate the efficacy and safety of different phosphate binders, including lanthanum carbonate, in children with CKD stages 4 to 5 and
- 5D. Possible end points include biochemical markers of bone and mineral metabolism, growth and nutritional status, and arterial morphology and function.

Recommendation 8: Fluid and Electrolyte Requirements and Therapy

Research Recommendations

- Studies to determine the optimal level of sodium and potassium restriction to control blood pressure and hyperkalemia in children of different ages or body sizes are needed.
- Studies to identify the best counseling and motivational methods to improve dietary adherence to dietary restriction of fluid, sodium, and potassium are required.

Recommendation 9: Carnitine

Research Recommendations

- Prospective studies should be conducted to evaluate the impact of carnitine therapy on the cardiac structure/function of patients with CKD stage 5D.
- Additional studies should evaluate the influence of long-term (> 6 months) treatment of anemia hyporesponsive to erythropoiesis-stimulating agents with L-carnitine supplementation.
- Further definition of the L-carnitine response should be studied by taking an outcomes approach to patients treated with L-carnitine. Can patient groups be identified who are likely to respond to L-carnitine for 1 or more of its proposed indications? Are certain individuals uniform responders across indications or do certain patient characteristics predict specific responses?

Recommendation 10: Nutritional Management of Transplant Patients

Research Recommendations

- Determine energy and protein requirements of children on corticosteroid therapy after transplantation.
- Determine whether dietary intervention is effective in minimizing posttransplantation weight gain, and if so, methods to motivate children to embrace a heart-healthy diet and regular exercise after transplantation.
- Determine whether posttransplantation calcium and vitamin D supplementation in children on corticosteroid therapy positively impact on bone mineral density and decrease the risk of osteopenia, osteoporosis, avascular necrosis, and fractures.

Research Recommendations

Guideline 2: Management of Hyperglycemia and General Diabetes Care in CKD

- Determine effects of glycemic control on early and late GFR loss and health outcomes of CKD. Evaluate different levels of glycemic control to optimize safety as well as clinical outcomes of survival, hospitalization, and CVD events in advanced CKD and/or ESRD.
- Perform validation studies of HbA1c, glycated albumin, and potentially other markers of long- term glycemic control in patients with diabetes and various stages of CKD.
- Assess metformin safety in patients with CKD stages 4 and 5.

Guideline 4: Management of Dyslipidemia in Diabetes and CKD

- Perform clinical trials of statins for primary and secondary prevention of CVD in patients with diabetes and CKD stages 1-4 and meta- analyses of completed studies in CKD stage 5.
- Conduct studies of other lipid-lowering agents for primary and secondary prevention of CVD, or patient level meta-analyses of completed studies, in patients with diabetes and CKD stages 1-4.
- Establish LDL-C levels for treatment and initia- tion of therapy as well as targets for primary and secondary prevention in patients with diabetes by CKD stage.
- Evaluate lipid-lowering therapy for CVD in patients with diabetes who are treated by hemo- dialysis or peritoneal dialysis, or who have received a kidney transplant.
- Examine results of previous studies, e.g., SHARP, by CKD stage.
- Examine data from completed clinical trials to assess effects of lipid lowering agents on out- comes such as albuminuria, eGFR, and ESRD in participants with diabetes.
- Examine lipid-lowering therapy for CVD in adolescent patients with diabetes.

Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes

- Durability of RAS inhibition for the delay in microalbuminuria onset should be tested by a treatment washout phase of at least two months duration.
- Post hoc adjustment for blood pressure differ- ences may be fraught with faulty assumptions. Therefore, equivalent blood pressure levels are an important design element to be considered in future clinical trials that test specificity of a drug's mechanism of action independent of blood pressure effects.

- Since the “endpoint” of preventing incident albuminuria derives validity from predicting increased risk of GFR loss, treatments to reduce albuminuria should not be offset by greater GFR decline. Measurement of GFR (e.g., eGFR or other more precise methods) should be per- formed as a companion to albuminuria. In clinical trials to demonstrate prevention of el- evated albuminuria, the demonstration of nor- moalbuminuria at baseline should follow wash- out of at least of two months duration from previous RAS blockade, with careful blood pressure control by alternative antihypertensive agents. This approach is necessary to avoid randomization of participants in whom albumin- uria is already present, but masked by RAS treatment, an effect which may be posited in several studies where there was rapid progres- sion to microalbuminuria in the first few months after randomization to placebo.
- Given the limitations of albuminuria as an outcome measure and the recent consensus panel’s recommendation against acceptance of albuminuria as a surrogate outcome, studies are needed to evaluate durability of effects on urinary albumin excretion. The categorization of albuminuria outcomes should be based on a minimum of two of three consecutive urine samples being in the same category.
- Consider an indication for regulatory approval based on demonstration of a lasting reduction in urinary albumin excretion, but conditional upon firm commitment to continue long-term studies to determine effects on GFR loss and clinically relevant outcomes.
- Evaluate the relative roles of ACE-Is, ARBs, renin blockers, and mineralocorticoid receptor blockers on progression of DKD in patients with albuminuria.
- Kidney biopsy outcomes based on carefully measured structural variables that correlate strongly with GFR loss may reduce the duration of primary prevention or early intervention DKD clinical trials. Consider enzyme replace- ment for Fabry’s Disease as an example.
- Clinical trials represent important opportunities to advance knowledge beyond addressing the primary hypotheses themselves. Protocols should include plans for acquiring and banking blood, urine, DNA, and other samples for eventual biomarker discovery and validation. Consider the DCCT as an example.

Research Recommendations

Because the process of guideline development involves a systematic review of the literature, it also identifies gaps in the evidence and raises important questions for future research. We list several research questions identified by the KDIGO guidelines that have direct relevance for the care of patients with CKD and HCV infection in the United States.

Guideline 1: Research Recommendations

- Knowledge of the pretest probability of HCV in different CKD populations is essential for a better understanding of the utility of both screening and follow-up testing of patients. A study to examine the prevalence of HCV infection in patients with various stages of CKD would allow better assessment of the utility and costs of screening and possibly support a rationale for testing in targeted settings.
- Rates of seroconversion for HCV of long-term HD patients should be defined in US dialysis centers.
- Cost-effectiveness studies should be performed to clarify the optimal pretest prevalence above which initial NAT testing should be used.

Guideline 2: Research Recommendations

CKD Non-HD Populations

- Studies are needed in HCV-infected patients with CKD Stages 3 to 5 without HCV-related kidney disease to identify the optimal treatment strategy.
- Trials also should be performed to determine the best treatment regimen for patients with HCV-associated glomerular diseases with and without cryoglobulinemia.

HD Populations

- Only 1 study has investigated treatment options for patients on HD therapy in the United States, and a large multicenter trial comparing different treatment regimens would be useful. These studies should evaluate both SVR and clinical outcomes, such as mortality. Patients African-American descent need to be represented in the studies because they make up 37% of the HD population and have greater rates of HCV infection[4] and lower response rates to treatment.
- Trials also should generate observational data for identification of factors predictive of SVR and long-term clinical outcomes after SVR to help select successful treatment candidates.

Kidney Transplant Populations

- Few treatment options for patients with HCV infection are available for kidney transplant recipients. Future studies should consider new agents or combinations of treatments designed to maximize efficacy while minimizing adverse events. The inclusion of kidney transplant recipients in studies of new medications and strategies should be encouraged.

Guideline 3: Research Recommendations

- Studies should be performed in US HD centers using molecular epidemiology methods to clarify whether nosocomial infection in the United States occurs from contact with the external surfaces of the dialysis apparatus or through the internal pathways, with special emphasis on the potential impact of dialyzer reuse practices on nosocomial transmission of HCV infection.

Guideline 4: Research Recommendations

- A registry should track clinical outcomes of HCV RNA–positive recipients who underwent transplantation of an HCV-infected deceased donor kidney to determine the risk of adverse outcomes.

Guideline 5: Research Recommendations

- The epidemiology of HCV-associated glomerular diseases needs to be better characterized in terms of prevalence, pathological variants, and the causal connection with HCV.

Research Recommendations

- The KDIGO guideline document summarizes our current knowledge regarding the management of CKD-MBD and highlights areas in need of future research. Each guideline chapter contains research recommendations at the end, and chapter 6 contains a short list of research questions deemed to have high priority for advancing the field. Research comparing therapeutic strategies for CKD-MBD admittedly is difficult to do because phosphate-lowering drugs, vitamin D and its analogues, calcimimetics, and dialysis calcium concentrations variably impact on the components of MBD. However, key questions are to what target phosphorus levels should be decreased in patients with CKD stages 3-5 and 5D and what the optimal treatment strategy is for this. Similarly, a key question is to what PTH target we should treat and with what strategy. In a population with a great burden of mortality and morbidity, treatment trials have to examine clinical end points.

- Future treatment trials also should examine surrogate outcomes along with clinical outcomes because reliance on surrogate end points requires validation by showing concordance with clinical outcomes in trials of similar agents or strategies in addition to robust risk relationships in observational studies.

Research Recommendations

- At the end of each section, members of the KDIGO work group made several suggestions for areas of future research. Our KDOQI work group agreed with the critical importance of research in these areas to create evidence upon which future recommendations and guidelines can be based.