AJKD
KDOQI Commentary

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD

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The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for evaluation, classification, and stratification of chronic kidney disease (CKD) was published in 2002. The KDOQI guideline was well accepted by the medical and public health communities, but concerns and criticisms arose as new evidence became available since the publication of the original guidelines. KDIGO (Kidney Disease: Improving Global Outcomes) recently published an updated guideline to clarify the definition and classification of CKD and to update recommendations for the evaluation and management of individuals with CKD based on new evidence published since 2002. The primary recommendations were to retain the current definition of CKD based on decreased glomerular filtration rate or markers of kidney damage for 3 months or more and to include the cause of kidney disease and level of albuminuria, as well as level of glomerular filtration rate, for CKD classification. 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.
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FOREWORD

It has been 12 years since the publication of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for evaluation, classification, and stratification of chronic kidney disease (CKD).[1] While not a new medication, a new device, or a landmark clinical trial, this guideline publication perhaps had a greater impact on the diagnosis and management of people with CKD than anything else that has happened in nephrology in the first decade of the 21st century. But like much in medicine, new "discoveries"—medications, devices, or clinical practice guidelines—need a test of time to understand their risks, benefits, and overall place in the care of patients. As the KDOQI CKD guideline made its way into clinical practice, much changed; creatinine assays were standardized, laboratory reports changed, new *International Classification of Diseases* (*ICD-9*) codes were generated, new equations for the estimation of glomerular filtration rate (GFR) were developed, nephrologists and others began to speak a common language when it came to studying and taking care of those with CKD, and an explosion in CKD-related research occurred. However, there was also concern that patients who did not have clinically meaningful kidney dysfunction were being identified as having a "disease," patients worried (stage 3 cancer is often life-threatening…stage 3 CKD cannot be much different), the inherent imprecision of formulas used to calculate estimated GFR (eGFR) for CKD classification was often underappreciated, and stage 5 CKD came to be interpreted by some as "time for dialysis." New information also became available, notably that albuminuria, not part of the 2002 NKF-KDOQI guideline CKD classification schema, was itself an independent predictor of important clinical outcomes and that a more precise degree of risk prediction became available as the result of innovative international research collaborations.

Thus, it became clear that a revision of the 2002 guideline was in order. The organization Kidney Disease: Improving Global Outcomes (KDIGO)

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convened a controversies conference in 2009 and subsequently organized an international work group to review and update the NKF-KDOQI CKD guideline. After the international KDIGO guideline was published in 2013,[2] NKF-KDOQI organized its own work group to provide a US-focused commentary on the KDIGO guideline. The yeoman efforts of this work group, led expertly by Drs Harold Feldman and Lesley Inker, are now presented in this commentary. The work group included experts in clinical nephrology, clinical epidemiology, and primary care medicine, and their many countless hours of volunteer work are much appreciated.

As has been stated many times, guidelines are guides to practice; they are not rules, they do not replace clinical judgment, they cannot anticipate patient preferences, and they are not able to speak to every conceivable clinical circumstance. They are also static, while medicine is not. Nonetheless, we believe that this NKF-KDOQI commentary will prove useful to physicians, nurses, and others involved in the care of patients with CKD.

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INTRODUCTION

The NKF-KDOQI guideline for evaluation, classification, and stratification of CKD from 2002 defined CKD as an abnormality of kidney structure or function regardless of cause or specific clinical presentation and proposed a staging system based on the level of GFR.[1] The guideline also suggested a conceptual model for the natural history of CKD that often begins with initial kidney damage and progresses through the stages of CKD toward the outcome of kidney failure. During this progression, individuals are at an elevated risk of cardiovascular disease (CVD) and death. This conceptual model highlights the clinical value of early identification and management of patients with CKD and has promoted broad-based reporting of eGFR by clinical laboratories to maximize the detection of occult CKD. The KDOQI guideline was well accepted by the medical and public health communities and led to much change in clinical practice within the primary care, nephrology, and other specialty communities.[3] However, the KDOQI guideline also stimulated some controversies and questions. In particular, there have been concerns that use of its definition of CKD has caused excessive false identification of CKD and that its staging system was not sufficiently informative about prognosis.[4]

In 2003, KDIGO was established with the mission "to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines."[5] Prior to embarking on a new guideline, KDIGO often holds conferences to review outstanding questions and available evidence for the purpose of assessing whether a new practice guideline is warranted. KDIGO convened such a conference in 2009, with the goal of addressing the shortfalls of the KDOQI staging system.[6] Analyses performed for the purpose of this conference demonstrated that GFR and albuminuria are independent and complementary predictors of important clinical outcomes, including CKD progression, end-stage renal disease (ESRD), acute kidney injury (AKI), cardiovascular mortality, and all-cause mortality.[7-10]

On the basis of these and other data that have been reported since the publication of the original 2002 KDOQI guideline, KDIGO formed a work group to develop an updated CKD guideline for the international community. The specific goals of the KDIGO CKD guideline update were to clarify the definition and classification system of CKD and to develop appropriate guidance for the management of individuals with CKD.[2] The primary recommendations were to retain KDOQI's use of GFR as the principal basis for staging CKD, but to augment the staging scheme by incorporating cause of kidney disease and level of albuminuria in addition to level of GFR. The KDIGO guideline update contains a discussion of CKD progression, recommendations regarding referral to nephrologists, and management of the complications of CKD.

REVIEW AND APPROVAL PROCESS FOR THIS COMMENTARY

To assist US practitioners in interpreting the KDIGO guideline, the NKF-KDOQI convened a work group to write a commentary. The commentary addresses the full scope of the KDIGO guideline, focusing in particular on their relevance to and implementation in the United States. The NKF-KDOQI Steering Committee first selected Co-Chairs and then individual members based on their clinical and/or research expertise and interest in the guideline process. Individual sections focusing on each of the topic areas of the KDIGO guideline were drafted by groups of coauthors based on detailed review of each of the KDIGO chapters supplemented by additional literature review. All KDOQI commentary work group members conferred regularly by teleconference, and consensus among coauthors was achieved through discussion. A detailed discussion of the cost implications of the

Box 1. Summary and Key Points

- The commentary on Chapter 1 addresses the definition and classification of CKD, agrees with the addition of the albuminuria stages, but raises concerns about the incorporation of cause of disease into staging and also highlights issues regarding use of GFR estimation and albuminuria in clinical practice
- The commentary on Chapter 2 addresses the definition and identification of progression and highlights the limitation of the proposed definitions of CKD for assessing progression of kidney disease
- The commentary on Chapter 3 addresses the management of progression and complications of CKD, and highlights recommendations to lower blood pressure goals in the setting of proteinuria and the limited evidence supporting the impact of various components of lifestyle modification
- The commentary on Chapter 4 addresses cardiovascular disease risk and highlights the need for individualized decision making in some circumstances, and emphasizes that care of patients with progressive CKD should include multiple caregivers
- The commentary on Chapter 5, addressing the referral to specialists and models of care, highlights the need for individualized decision making in some circumstances, and that care of patients with progressive CKD should include multiple caregivers.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

recommendations is not included in this commentary. This document was reviewed and approved by all coauthors and the KDOQI leadership.

The structure of this commentary aligns with the structure of the KDIGO guideline.[2] Numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original (all material is reproduced with permission of KDIGO). The text that follows, written by the commentary work group, comments on key guideline recommendations and discusses their implementation in the United States (see Box 1 for an overview).

DEFINITION AND CLASSIFICATION OF CKD

Definition of CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (*Not Graded*) [See table titled "Criteria for CKD (either of the following present for >3 months)"]

Commentary

A formalized definition of CKD has provided great benefit to public health education efforts, research, and funding policies. The definition of CKD remains largely unchanged from previous guidelines, but has been clarified by the addition of "with implications for health," recognizing that not all abnormalities are similarly related to outcomes. The commentary work group concluded that not all structural or functional changes of the kidney have implications for health and that it is often not possible to accurately predict which patients will be negatively impacted. The classic example is the otherwise healthy kidney donor who has a GFR of 55 mL/min/1.73 m^2. There are minimal implications for this person's health, but some medications may need dose adjustment and there may be side effects from long-term nonsteroidal anti-inflammatory drug (NSAID) usage. Finally, we concur with the criterion of kidney abnormalities being present for at least 3 months as a means of discriminating between chronic and acute disease, both in clinical practice and research studies. The duration of abnormalities has commonly been ignored in research studies.

Staging of CKD

1.2.1: We recommend that CKD is classified based on cause, GFR category, and albuminuria category (CGA). (*1B*)

1.2.2: Assign cause of CKD based on presence or absence of systemic disease and the location within the kidney of observed or presumed pathologic-anatomic findings. (*Not Graded*)

1.2.3: Assign GFR categories as follows (*Not Graded*) [See table titled "GFR categories in CKD"]

1.2.4: Assign albuminuria* categories as follows (*Not Graded*) [See table titled "Albuminuria categories in CKD"]
*note that where albuminuria measurement is not available, urine reagent strip results can be substituted.

Commentary

Numerous studies in recent years have provided convincing evidence that both lower GFR and greater levels of albuminuria are independently related to mortality, cardiovascular events, and the rate of ESRD. As reviewed in the guideline, greater levels of

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

albuminuria are strongly predictive of outcomes at all levels of GFR at the individual and population levels.[6-10] Integrating both GFR and albuminuria into CKD staging paradigms will hopefully provide more precise classification and more accurate prognostic information. The commentary work group supports the addition of albuminuria into the classification scheme of CKD and characterization of the level of albuminuria by its severity (see last column in the table titled "Albuminuria categories in CKD"), rather than the terms microalbuminuria or macroalbuminuria.

We endorse the new distinction between CKD stage 3a (GFR of 45-59 mL/min/1.73 m^2) and 3b (GFR of 30-44 mL/min/1.73 m^2) in the updated guideline. As reviewed in the guideline, the risks of mortality and other outcomes vary greatly between these groups. The high prevalence of CKD stage 3 suggests that this distinction will have broad applications.

In contrast, the commentary work group views it premature to add cause of CKD to the classification scheme, although some specific causes have been related to faster rates of CKD progression and other health outcomes. Notably, there are currently no accurate methods to quantify risk based on cause of disease. The commentary work group considers that incorporating this information into the classification scheme could limit the ease of understanding and applicability of the classification scheme for referring physicians. (See chapter 5 of the KDIGO guideline for discussion of the inclusion as specific causes or unknown causes as reason for referral.)

The KDIGO guideline does not address screening for CKD among specific populations. However, we thought it would be worthwhile to comment on this topic given that the recent US Preventive Services Task Force recommendation highlighted the current lack of sufficient evidence to support CKD screening of asymptomatic adults.[11] A subsequent statement by the American College of Physicians (ACP) qualified these recommendations, saying that asymptomatic adults who are not at high risk for CKD should not be screened. The ACP went on to recommend not screening for proteinuria those individuals who are currently taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Separate guideline recommendations for patients with specific conditions placing them at higher risk of CKD (ie, diabetes or hypertension) suggest routine screening may be useful, but testing strategies and specific recommendations vary.[12,13] The 2002 KDOQI guideline recommended assessment of the risk for developing CKD for all individuals, with measurement of blood pressure, albuminuria, and serum creatinine to estimate the GFR among those at higher risk. The commentary work group endorses the recommendations from the original guideline for screening among individuals at high risk for CKD despite the absence of this specific recommendation in the KDIGO guideline (Box 2), and as such is in agreement with the recommendation of the ACP to

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR > 2220 mg/g; >220 mg/mmol]).

Box 2. Potential Risk Factors for Susceptibility to and Initiation of CKD

Clinical Factors
- Diabetes
- Hypertension
- Autoimmune diseases
- Systemic infections
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Neoplasia
- Family history of chronic kidney diseases
- Recovery from acute kidney failure
- Reduction in kidney mass
- Exposure to certain drugs
- Low birth weight

Sociodemographic Factors
- Older age
- US ethnic minority status: African American, American Indian, Hispanic, Asian or Pacific Islander
- Exposure to certain chemical and environmental conditions
- Low income/education

Abbreviation: CKD, chronic kidney disease.

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screen asymptomatic adults only if they are at high risk for CKD. However, the commentary work group thought that information is gained from knowledge of the level of proteinuria beyond decisions to treat with an ACE inhibitor/ARB, such as prognosis and therefore disagrees with the ACP's recommendation to not screen individuals treated with ACE-inhibitor/ARB agents.

Prognosis and Evaluation of CKD (Recommendations 1.3-1.4.3.8)

1.3 PREDICTING PROGNOSIS OF CKD

1.3.1: In predicting risk for outcome of CKD, identify the following variables: 1) cause of CKD; 2) GFR category; 3) albuminuria category; 4) other risk factors and comorbid conditions. (*Not Graded*)

1.3.2: In people with CKD, use estimated risk of concurrent complications and future outcomes to guide decisions for testing and treatment for CKD complications. (*Not Graded*)

1.3.3: In populations with CKD, group GFR and albuminuria categories with similar relative risk for CKD outcomes into risk categories. (*Not Graded*) [See Figure titled "Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012"]

1.4 EVALUATION OF CKD

1.4.1: *Evaluation of chronicity*

1.4.1.1: In people with GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)
- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

1.4.2: *Evaluation of cause*

1.4.2.1: Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease. (*Not Graded*)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

1.4.3: *Evaluation of GFR*

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (*1A*)

1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (*2B*)

1.4.3.3: We recommend that clinicians (*1B*):
- use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.
- understand clinical settings in which $eGFR_{creat}$ is less accurate.

1.4.3.4: We recommend that clinical laboratories should (*1B*):
- measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.
- report $eGFR_{creat}$ in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting $eGFR_{creat}$.
- report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.

When reporting serum creatinine:
- We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (μmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl).

When reporting $eGFR_{creat}$:
- We recommend that $eGFR_{creat}$ should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.
- We recommend $eGFR_{creat}$ levels less than 60 ml/min/1.73 m^2 should be reported as "decreased."

1.4.3.5: We suggest measuring cystatin C in adults with $eGFR_{creat}$ 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage if confirmation of CKD is required. (*2C*)
- If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is also $<$60 ml/min/1.73 m^2, the diagnosis of CKD is confirmed.
- If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is $\geq$60 ml/min/1.73 m^2, the diagnosis of CKD is not confirmed.

1.4.3.6: If cystatin C is measured, we suggest that health professionals (*2C*):
- use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.
- understand clinical settings in which $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ are less accurate.

1.4.3.7: We recommend that clinical laboratories that measure cystatin C should (*1B*):
- measure serum cystatin C using an assay with calibration traceable to the international standard reference material.
- report eGFR from serum cystatin C in addition to the serum cystatin C concentration in adults and specify the equation used whenever reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$.
- report $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively, or alternative cystatin C-based GFR estimating equations if they have been shown to improve accuracy of GFR estimates compared to the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.

When reporting serum cystatin C:
- We recommend reporting serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/l).

When reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$:
- We recommend that $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.
- We recommend $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ levels less than 60 ml/min/1.73 m^2 should be reported as "decreased."

1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions. (*2B*)

Commentary

This section focuses primarily on the aspects of evaluation of GFR and albuminuria that are relevant for clinicians. Although the guideline also discusses evaluation for chronicity and cause, the commentary work group agrees with these statements and does not have any additional comments.

Estimation of GFR from serum creatinine remains the clinical standard worldwide. Consistent with the original KDOQI CKD guideline, the KDIGO guideline emphasizes the importance of estimation of GFR rather than use of serum creatinine concentration alone.[1,2] The guideline also recognizes the limitations of creatinine and recommends additional confirmatory tests, such as measurement of cystatin C or clearance in situations when estimates of GFR from serum creatinine are less accurate.

The commentary work group agrees with the recommendation to use GFR estimating equations rather than creatinine alone for evaluation of kidney function. The commentary work group supports ongoing efforts to promote the use of specific creatinine assays calibrated to international standard reference materials with minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference materials.[14] In addition, the commentary work group encourages the use of the CKD-EPI (CKD Epidemiology Collaboration) creatinine 2009 equation or other similarly accurate equations.[15]

The KDIGO guideline also describes uses of cystatin C, alone or in combination with creatinine, to estimate GFR. The guideline does not state explicitly whether GFR should be estimated from cystatin C

alone or in combination with creatinine. For the purposes of estimation of measured GFR, the combination of both markers provides a more precise estimate.[16-19] For determination of prognosis and risk stratification, the evidence is less certain.[20] We agree with reporting both $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ whenever cystatin C and creatinine are ordered so that the clinician can have both values of eGFR available for decision making.

The KDIGO guideline recommends measurement of cystatin C in persons with $eGFR_{cr}$ of 45-59 mL/min/1.73 m^2 without albuminuria. The rationale for this statement is based on data showing that eGFR from creatinine may misclassify CKD and studies showing that GFR estimates using cystatin C in combination with creatinine improve classification of CKD based on measured GFR.[17] The guideline states that among persons with $eGFR_{cr}$ of 45-59 mL/min/1.73 m^2 without albuminuria and whose $eGFR_{cr\text{-}cys}$ and/or $eGFR_{cys}$ values are >60 mL/min/1.73 m^2, the risk for CKD complications is very low. These persons could be considered not to have CKD. In addition, the guideline work group states that prediction of risk for future adverse events is improved with the use of cystatin C–based GFR estimates, as is supported by several studies, including a large meta-analysis published after the guideline; however, no specific recommendation was made by KDIGO.[20]

We agree that GFR estimation using cystatin C alone or in combination with creatinine is useful as a confirmatory test of eGFR from creatinine, and that it improves risk stratification. However, many questions remain regarding how to incorporate cystatin C–based GFR estimates into practice. The KDIGO guideline mentions only one specific circumstance, but eGFR is used in multiple clinical settings on a routine basis and the guideline does not address most of these. For example, whether creatinine- or cystatin C–based estimates should be used to follow up patients longitudinally after the initial diagnosis is made remains unaddressed. In the commentary work group's opinion, assuming a patient remains clinically stable, it seems reasonable to use cystatin C–based eGFR estimates at subsequent time points, although there are no data to support this statement at this time.

Implementation

1. Practical issues related to cystatin C measurement need to be considered prior to its introduction into the community at large. Notably, the price of testing is steadily decreasing, measurement is now automated, and it can be performed on existing platforms without the need for specialized equipment. More importantly, only cystatin C measurements obtained using assays traceable to higher level reference materials should be used to estimate the GFR.

2. The availability of measured GFR as a confirmatory test for eGFR from creatinine is limited by the lack of *Current Procedural Terminology* (*CPT*) codes for nonradioactive exogenous filtration markers, which precludes its financial viability. In addition, reference materials for nonradioactive iothalamate or iohexol are not available, further limiting their widespread use.

Evaluation of Albuminuria

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (*2B*);
1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than concentrations alone. *(1B)*

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

1.4.4.3: Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Grade*d):
- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.
- Confirm ACR ≥ 30 mg/g (≥3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.
- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

1.4.4.4: If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., α_1-microglobulin, monoclonal heavy or light chains, [known in some countries as "Bence Jones" proteins]). (*Not Graded*)

Commentary

The guideline recommends urinary albumin-creatinine ratio (ACR) in spot urine samples as the preferred measure rather than urine protein or albumin. The rationale for this recommendation is that ACR is a more sensitive and specific measure of kidney damage. Another motivation for this recommendation is that there are ongoing standardization efforts for urine albumin, whereas urine protein is more difficult to standardize.[21] The commentary work group agrees with this recommendation.

There are many factors that can affect urine protein or albumin temporarily. Some factors are related to specimen collection technique (eg, menstrual blood

Table 1. Factors Affecting Urinary ACR

Factor	Examples of effect
Preanalytical factors	
Transient elevation in albuminuria	Menstrual blood contamination
	Symptomatic UTI[69]
	Exercise[70]
	Upright posture (orthostatic proteinuria)[71,72]
	Other conditions increasing vascular permeability (e.g., septicemia)
Intraindividual variability	Intrinsic biological variability[73]
	Genetic variability[74]
Preanalytical storage conditions	Degradation of albumin before analysis[a]
Non-renal causes of variability in creatinine excretion	Age (lower in children and older people)
	Race (lower in Caucasian than black people)
	Muscle mass (e.g., lower in people with amputations, paraplegia, muscular dystrophy)
	Gender (lower in women)
Changes in creatinine excretion	Non-steady state for creatinine (AKI)
Analytical factors	
Antigen excess ('prozone') effect	Samples with very high albumin concentrations may be falsely reported as low or normal using some assays[75]

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; UTI, urinary tract infection.

[a]Samples for urinary albumin (or total protein) measurement may be analyzed fresh, stored at 4°C for up to 1 week, or stored at −70°C for longer periods. Freezing at −20°C appears to result in loss of measurable albumin and is not recommended. When analyzing stored samples, they should be allowed to reach room temperature and be thoroughly mixed prior to analysis.[76]

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contamination) and others are related to numerous physiologic factors unrelated to renal function or injury (eg, exercise, urinary tract infection; shown in Table 1). Education of clinicians for these causes of variability in measured ACR levels other than changes in the level of kidney damage is necessary to promote appropriate interpretation of proteinuria data.

Because untimed urinary collections are difficult to standardize, concentrations of albumin or protein from such collections can be misleading. Measurement in the first morning urine is preferred because its protein concentration correlates well with 24-hour protein excretion and has relatively low intraindividual variability. Reporting of the albumin or total protein as a ratio indexed to the urine creatinine helps account for the variability in urinary albumin or total protein concentration measured in spot samples due to changes in urinary concentration. Assuming a creatinine excretion of 1 g/d, an ACR of 1,000 mg/g would translate to an albumin excretion rate (AER) of 1,000 mg/d. However, this assumption is not correct. Development of validated estimating equations for creatinine excretion that account for variation in urinary creatinine among people may be helpful to provide ACR or protein-creatinine ratio (PCR) values that are accurate estimates of total albumin or protein excretion. Last, we endorse the elimination of "microalbuminuria" and "macroalbuminuria" from the diagnostic testing lexicon.

Implementation

Clinicians may be resistant to switching from urine protein to urine albumin since little evidence exists in the current medical literature for a difference in the value of these measures in predicting clinical outcomes. Educational efforts on the value of using urine albumin, in particular related to assay methodological issues, may be required.

DEFINITION, IDENTIFICATION, AND PREDICTION OF CKD PROGRESSION

Definition and Identification of CKD Progression

2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions. *(Not Graded)*

2.1.2: Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (*Not Graded*)

2.1.3: Define CKD progression based on one of more of the following (*Not Graded*):

- Decline in GFR category (≥90 [G1], 60–89 [G2], 45–59 [G3a], 30–44 [G3b], 15–29 [G4], <15 [G5] ml/min/1.73 m^2). A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.
- Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/yr.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

2.1.4: In people with CKD progression, as defined in Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. *(Not Graded)*

Commentary

None of the recommendations in this chapter are graded. Despite having no evidence base, these recommendations have some face validity and address an important area, categorization of rates of kidney disease progression. We agree with the guideline statement that the frequency of estimating GFR and measuring albuminuria should increase with severity of

Table 2. Decline in Kidney Function in CKD Populations

Study	Study population	*N*	Baseline GFR ml/min/1.73 m^2	Mean Follow-up years	GFR decline, Mean (SD) or (95% CI) ml/min/1.73 m^2/year
			Mean (SD)		
MDRD Study Group[77]	Study A: GFR 25-80 ml/min/1.73 m^2	28	37.1 (8.7)	1.2	3.7 (7.6)
	Study B: GFR 7.5-24 ml/min/1.73 m^2	63	15.0 (4.5)		4.3 (4.7)
Klahr S et al.[78]	Study 1: GFR 25-55 ml/min/1.73 m^2		Mean (SD)	2.2 years	
	- Usual protein, usual MAP	145	37.6 (9.0)		4.5 (3.7–5.3)
	- Usual protein, low MAP	149	38.2 (8.6)		3.3 (2.5–4.1)
	- Low protein, usual MAP	140	38.9 (8.8)		3.3 (2.5–4.2)
	- Low protein, low MAP	151	39.7 (9.1)		2.3 (1.5–3.0)
	Study 2: GFR 13-45 ml/min/1.73 m^2				
	- Low protein, usual MAP	62	18.7 (3.1)		4.9 (3.8–5.9)
	- Low protein, low MAP	67	18.8 (3.3)		3.9 (3.2–4.7)
	- Very low protein, usual MAP	61	18.3 (3.7)		3.6 (2.8–4.4)
	- Very low protein, low MAP	65	18.4 (3.5)		3.5 (2.6–4.5)
Wright J et al.[79]	African Americans with hypertension and GFR 20-65 ml/min/1.73 m^2		Mean (SD)	4 years	Mean (SE)
	- Low MAP	380	46.0 (SD 12.9)		2.21 (0.17)
	- Usual MAP	374	45.3 (SD 13.2)		1.95 (0.17)
Eriksen B[80]	GFR categories G3a-G3b (GFR 30-59 ml/min/1.73 m^2)	3047	Median (IQR) 55.1 (50.8–57.9)	Median 3.7 years	Mean 1.03 ml/min/1.73 m^2/yr
Jones C et al.[81]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	726	Median (IQR) 29 (18-38)	Median (IQR) 2.9 years (1.3–4.1)	Median 0.35 ml/min/1.73 m^2/yr
Levin A et al.[82]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	4231	Median 33 ml/min/1.73 m^2	Median (IQR) 2.6 years (1.6-3.6)	Mean 2.65 ml/min/1.73 m^2/year

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; SE, standard error.

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disease. The commentary work group also agrees that it is important to recognize the inherent variability of creatinine when interpreting change in eGFR.

However, the commentary work group is concerned about the proposed magnitude of change in eGFR that signals disease progression for the following reasons. First, a definition based on percentage reduction of eGFR will differ across starting levels of eGFR and the duration of time over which the changes occur. For example, a 25% reduction in eGFR when beginning with levels such as 60 mL/min/1.73 m^2 would imply a loss of 15 mL/min/1.73 m^2, a substantial loss of kidney function if it occurred over a relatively short time (eg, 2 years). Second, this amount of change is greater than the mean annual decline in eGFR found in any of the studies among individuals with CKD reported (Table 2) and is greater than the third criterion listed by the KDIGO guideline as indicating rapid progression (≥5 mL/min/1.73 m^2 per year). Indeed, the evidence described in the KDIGO guideline from the Alberta Kidney Disease Network suggests that a decline of <25% is also associated with increased risk of all-cause mortality and ESRD (Table 3).[2,22-24] Third, changes in eGFR may be secondary to progression of CKD or superimposed AKI, and these often cannot be differentiated by considering a single value. Use of this stringent cutoff point for clinical decision making, such as referral as described in chapter 5 of the KDIGO guideline, may lead referring physicians to avoid

Table 3. CKD Progression and Risk of All-Cause Mortality and ESRD Using Baseline (first) eGFR

Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	**Ref**	**Ref**
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio.

*ESRD defined as requiring renal replacement therapy.

**Adjusted for age, gender, hypertension, diabetes, proteinuria, Charlson comorbidities and baseline (first) eGFR.

Data from Turin et al.[23,24]

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earlier and appropriate investigations of kidney disease.

Albuminuria is central throughout the KDIGO guideline for the definition and staging of disease, and elsewhere in this chapter it is stated that assessment of albuminuria "should be undertaken to evaluate progression."[2(p65)] Nevertheless, the severity of albuminuria or changes in albuminuria over time is not included in the proposed definition of progression. The KDIGO guideline justifies this by saying that there are no data to support specific cut points for change in albuminuria that are associated with kidney disease progression. The commentary work group agrees that changes in albuminuria should not be included in the definition of progression. However, if increases in albuminuria are not considered progression of CKD, the rationale for their measurement with a frequency similar to eGFR is not clear. The points made in chapter 1 of the KDIGO guideline about causes of variation in albuminuria are relevant here too when determining changes in albuminuria.

Regression of mild/moderate albuminuria is not uncommon, and discussion of how to evaluate remission of CKD with respect to both improvements in GFR and albuminuria is not included in the guideline.

Predictors of Progression

2.2.1: Identify factors associated with CKD progression to inform prognosis. These include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, ongoing exposure to nephrotoxic agents, and others. (*Not Graded*)

Commentary

The commentary work group agrees with the KDIGO guideline about the key factors that inform prognosis. We also agree that prediction models may be a valuable tool, but they should be validated in a wide variety of clinical settings to ensure their generalizability prior to widespread use.

Implementation

1. It is important to differentiate between progression of chronic disease and acute injury. The definitions of each are different. As the definition of CKD progression is currently written, small changes in GFR could be consistent with AKI, whereas only large changes in GFR would indicate progressive CKD. However, small changes may be consistent with progressive CKD rather than AKI. Clinicians will need to attend to other clinical indicators to be able to accurately identify the cause of changes in GFR. Education of non-nephrologists as to how to differentiate these clinical entities will be challenging.

2. Change in eGFR may be due to true change in GFR or due to changes in the non-GFR determinants of creatinine concentrations, including assay fluctuations. Differentiating between these requires serial assessments and consideration of potential changes in the non-GFR determinants of creatinine. Education of non-nephrologists as to how to differentiate these clinical entities will be challenging.

3. Use of validated prediction models for progression of kidney disease may be able to incorporate numerous clinical factors and provide a single prognostic metric, which can guide decisions. Incorporation of such models into laboratory systems may facilitate their use.

MANAGEMENT OF PROGRESSION AND COMPLICATIONS OF CKD

Prevention of CKD Progression (Recommendations 3.1.1-3.1.11)

BP and RAAS interruption

3.1.1: Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment as described in the KDIGO 2012 Blood Pressure Guideline. (*Not Graded*)

3.1.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (*Not Graded*)

3.1.3: Tailor BP treatment regimens in elderly patients with CKD by carefully considering age, comorbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. (*Not Graded*)

3.1.4: We recommend that in both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic. (*1B*)

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of ≥ 30 mg/24 hours (or equivalent) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. (*2D*)

3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (or equivalent). (*2D*)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion $>$ 300 mg/24 hours (or equivalent). (*1B*)

3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (*Not Graded*)

3.1.9: We recommend that in children with CKD, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (*1C*)

3.1.10: We suggest that in children with CKD (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (*2D*)

3.1.11: We suggest that an ARB or ACE-I be used in children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (*2D*)

Commentary

Section 3.1 of the KDIGO guideline reviews the evidence in support of the recommendations aimed at delaying CKD progression. Recommendations for management of blood pressure were derived from the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD.[25] These recommendations are based on moderately strong evidence, with most of them falling between level 1B and 2D. The guideline encourages individualized targets based on age and tolerability of the chosen regimen and also provides specific blood pressure targets based on level of albuminuria and comorbid conditions. For example, the recommended target blood pressure for patients with CKD without albuminuria is ≤140/90 mm Hg, whereas it is ≤130/80 mm Hg for patients with albumin excretion ≥ 30 mg/24 h. This represents a departure from the target recommended by the 2004 KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in CKD, which recommended ≤130/80 mm Hg for all patients with CKD.[26] Overall, we agree with these recommendations, but also note that the blood pressure goal of ≤130/80 mm Hg for individuals with albuminuria is based on relatively low-quality evidence (2D). The panel members appointed to the Eighth Joint National Committee (JNC 8) recently released the 2014 evidence-based guideline for the management of high blood pressure in adults.[27] In patients with CKD, they recommend initiation of treatment for blood pressures > 140/90 mm Hg for patients of all ages without differentiation of targets by level of proteinuria. Higher quality evidence regarding the safety and efficacy of intensive blood pressure control will be forthcoming from the ongoing National Institutes of Health–sponsored Systolic Blood Pressure Intervention Trial (SPRINT), which includes a CKD subgroup.[28]

The KDIGO guideline recommends an ACE inhibitor or ARB for patients with diabetes whose urinary albumin excretion is 30-300 mg/24 h and for all patients, with and without diabetes, whose urinary albumin excretion is >300 mg/24 h. We agree with the guideline-specific recommendations to use an ACE inhibitor or ARB and not the combination given the accumulating evidence of harm with combination therapy.[29]

Prevention of CKD Progression (Recommendations 3.1.12-3.1.18)

CKD and risk of AKI

3.1.12: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

3.1.12.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

Protein intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (*2C*) or without diabetes (*2B*) and GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5), with appropriate education.

3.1.14: We suggest avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression. (*2C*)

Glycemic control

3.1.15: We recommend a target hemoglobin A_{1c} (HbA_{1c}) of ~7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (*1A*)

3.1.16: We recommend not treating to an HbA_{1c} target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (*1B*)

3.1.17: We suggest that target HbA_{1c} be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (*2C*)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (*Not Graded*)

Commentary

The single level 1A guideline is derived from the KDOQI *Clinical Practice Guideline for Diabetes and CKD: 2012 Update*[30] that recommended a target hemoglobin A_{1c} (HbA_{1c}) in diabetes. Motivated by recent evidence of harm with intensive glycemic control,[31-33] the guideline recommends a target HbA_{1c} of ~7%, with the higher target for those with a limited life expectancy, comorbid conditions, or an elevated risk of hypoglycemia.

Prevention of CKD Progression (Recommendations 3.1.19-3.1.22)

Salt intake

3.1.19: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated (CKD). (*1C*)

3.1.19.1: We recommend restriction of sodium intake for children with CKD who have hypertension (systolic and/or diastolic blood pressure >95th percentile) or prehypertension (systolic and/or diastolic blood pressure >90th percentile and

<95th percentile), following the age-based Recommended Daily Intake. (*1C*)

3.1.19.2: We recommend supplemental free water and sodium supplements for children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth. (*1C*)

Hyperuricemia

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. *(Not Graded)*

Lifestyle

3.1.21: We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20 to 25, according to country specific demographics), and stop smoking. (*1D*)

Additional dietary advice

3.1.22: We recommend that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated. (*1B*)

Commentary

The guideline addresses dietary modifications and lifestyle changes in CKD. The commentary work group concurs with most of these recommendations with the following caveat. The recommendation to maintain a body mass index (BMI) of 20-25 kg/m^2 may be inappropriate for certain patients with CKD. Observational data suggest that the relationship between BMI and risk of adverse outcomes in CKD may be different from that in the general population.[34-36] Moreover, given the propensity for fluid retention in CKD, we thought that BMI may not accurately reflect body fat in this setting.[37] In addition, overly restrictive dietary prescriptions may diminish total caloric intake, markedly reduce protein intake, and result in malnutrition.

We agree with the ungraded statement that there is insufficient evidence to make recommendations for use of uric acid–lowering agents for the prevention of CKD progression.

Complications of CKD

3.2 COMPLICATIONS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION

Definition and identification of anemia in CKD

3.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

3.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12-15 years. (*Not Graded*)

Evaluation of anemia in people with CKD

3.2.3: To identify anemia in people with CKD measure Hb concentration (*Not Graded*):

- when clinically indicated in people with GFR ≥ 60 ml/min/1.73 m^2 (GFR categories G1-G2);
- at least annually in people with GFR 30–59 ml/min/1.73 m^2 (GFR categories G3a-G3b);
- at least twice per year in people with GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5).

3.3 CKD METABOLIC BONE DISEASE INCLUDING LABORATORY ABNORMALITIES

3.3.1: We recommend measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity at least once in adults with GFR < 45 ml/min/1.73 m^2 (GFR categories G3b-G5) in order to determine baseline values and inform prediction equations if used. (*1C*)

3.3.2: We suggest not to perform bone mineral density testing routinely in those with eGFR < 45 ml/min/1.73 m^2 (GFR categories G3b-G5), as information may be misleading or unhelpful. (*2B*)

3.3.3: In people with GFR < 45 ml/min/1.73 m^2 (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (*2C*)

3.3.4: In people with GFR < 45 ml/min/1.73 m^2 (GFR categories G3b-G5) the optimal PTH level is not known. We suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. (*2C*)

Vitamin D supplementation and bisphosphonates in people with CKD

3.3.5: We suggest not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated PTH concentrations in people with CKD not on dialysis. (*2B*)

3.3.6: We suggest not to prescribe bisphosphonate treatment in people with GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5) without a strong clinical rationale. (*2B*)

3.4 ACIDOSIS

3.4.1: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (*2B*)

Commentary

Previously published guideline statements on anemia[38] and CKD–mineral and bone disorder (CKD-MBD)[39] are included in the KDIGO CKD guideline and are mostly unchanged from these original publications. However, the recommendations for the use of vitamin D supplementation is more cautious than in KDIGO's CKD-MBD guideline,[39] with a suggestion to prescribe vitamin D supplementation only if there is evidence of documented deficiency. Use of bone mineral density

testing is discouraged in patients with GFR < 45 mL/min/1.73 m^2, and there is a suggestion not to prescribe bisphosphonates in patients with GFR < 30 mL/min/1.73 m^2. Use of bicarbonate supplements is suggested in patients with serum bicarbonate levels < 22 mmol/L. Tables 4 and 5 outline the use of phosphate binders and bisphosphonates, respectively.[39]

Although the recommendations in this section were not based on strong evidence, the commentary work group agreed with most of the guideline statements. We thought that there are insufficient data to endorse the recommendation to use markers of mineral metabolism in risk prediction models.

Implementation

1. There are multiple recommendations made for the management of CKD and it may be challenging to implement all of them for any one patient. Approaching the recommendations in this chapter with some flexibility may allow clinicians to identify aspects of the guideline that may be more applicable to individual patients with CKD and to modify treatment strategies over the course of care. In addition, evidence is strongest for recommendations related to management of diabetes and hypertension, which often complicate CKD. Thus, it would be justifiable to first devote effort to setting blood pressure and glycemic goals, tailor antihypertensive and hypoglycemic therapies to individual patients, and monitor for side effects of the medications.

2. Because reduction in dietary sodium may facilitate achievement of blood pressure goals and the widespread use of sodium in the US food supply,

Table 4. Phosphate-Binding Agents in Routine Clinical Practice and Their Ranked Cost

Agent	Dose/day	Clinical experience and evidence base	Ranked cost*
Aluminium hydroxide	1.425-2.85 g	Extensive clinical experience in CKD and ESRD, no RCT comparison versus placebo. Aluminium accumulates in bone and neural tissue with long-term use, avoids calcium	1
Calcium citrate	1.5-3 g	Limited trial evidence in ESRD. Reduction in phosphate and elevation in calcium dose-dependent	2
Magnesium carbonate	0.7-1.4 g (plus calcium carbonate 0.33-0.66 g)	Short-term RCT evidence in ESRD, less hypercalcemia	3
Calcium acetate and Magnesium carbonate combination	Calcium acetate 435 mg plus Magnesium carbonate 235 mg, 3-10 tablets daily	Short-term RCT evidence in ESRD, less hypercalcemia	3
Calcium carbonate	3-6 g	Extensive clinical experience in CKD and ESRD, limited RCT evidence versus placebo. Reduction in phosphate and elevation in calcium both dose-dependent	4
Calcium acetate	3-6 g	Extensive clinical experience in ESRD; RCT evidence comparing to other binders. Reduction in phosphate and elevation in calcium dose-dependent but less than with calcium carbonate	4
Lanthanum carbonate	3 g	Extensive prospective cohort evidence, RCT evidence compared to other phosphate binders. Potential for accumulation in bone and other tissues, avoids calcium	5
Sevelamer-HCl	4.8-9.6 g	Extensive prospective cohort evidence in ESRD; RCT evidence compared to other phosphate binders; surrogate and patient-centered outcomes, avoids calcium	6
Sevelamer carbonate	4.8-9.6 g	RCT evidence compared to other phosphate binders; equivalency studies compared to sevelamer-HCl, avoids calcium	6

Note: Data as of January 2013.

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; RCT, randomized controlled trial.

*The average annual cost of aluminium hydroxide in the UK, for example, is £51/year, equivalent to US$84/year. The cost of lanthanum and sevelamer in the UK is 38-42 times higher and the cost of calcium and magnesium-based binders 5-7 times higher than aluminium hydroxide (all drug costs derived from 2011 British National Formulary list prices).

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Table 5. Summary Data for Bisphosphonates and CKD

Agent	Indications	Dose, frequency and route of administration	Special considerations for CKD and clinical trial notes
Alendronate	Postmenopausal osteoporosis	10 mg daily, oral	GFR < 35 ml/min/1.73 m^2: not recommended
	Corticosteroid use	70 mg weekly, oral	No reported adverse events specific to CKD
Clodronate	Malignancy-related bone disease	1.6-3.2 g daily, oral	GFR < 10 ml/min/1.73 m^2: contraindicated GFR 10–30 ml/min/1.73 m^2: reduce dose by 50%
Etidronate	Postmenopausal osteoporosis	400 mg daily for 14 days, oral	Mild renal impairment: reduce dose
	Corticosteroid use	5-10 mg/kg daily for up to 6 months	Moderate or severe renal impairment: avoid
	Paget's disease		No data in CKD
Ibandronate	Malignancy-related bone disease	150 mg monthly, oral	GFR < 30 ml/min/1.73 m^2: not recommended
	Postmenopausal osteoporosis	3 mg every 3-months intravenous	No reported adverse events specific to CKD
Pamidronate	Malignancy-related bone disease	15-60 mg single dose, intravenous	GFR < 30 ml/min/1.73 m^2: avoid
	Paget's disease	30 mg weekly for 6 weeks, intravenous	AKI reported
Risedronate	Postmenopausal osteoporosis	5 mg daily, oral	GFR < 30 ml/min/1.73 m^2: contraindicated
	Corticosteroid use	35 mg weekly, oral	No reported adverse events specific to CKD
	Paget's disease		
Tiludronate	Paget's disease	400 mg daily for 3 months	CrCl < 30 ml/min: contraindicated No data in CKD
Zoledronate	Malignancy-related bone disease	4-5 mg single dose, intravenous	GFR < 30 ml/min/1.73 m^2: avoid
	Postmenopausal osteoporosis		GFR < 60 ml/min/1.73 m^2: graded dose reduction
	Paget's disease		No data in CKD, AKI reported in non-CKD

Note: Data as of January 2013.
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CrCl, creatinine clearance; GFR, glomerular filtration rate.
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it seems reasonable to incorporate counseling on dietary sodium reduction into routine management of hypertension. However, achieving this goal is extremely difficult, in part because measurement of the sodium intake is not easy to implement, often requiring a 24-hour urine collection. In addition, access to expert dietary counseling may be a challenge for most US predialysis CKD care settings with the current billing and payment structure for allied health care professions, including dietitians. Population-level interventions, including modifications of sodium content in processed foods, will be required to effect substantive reductions in sodium intake.[40]

OTHER COMPLICATIONS OF CKD

CKD and CVD

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (*1A*)

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (*1A*)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (*2B*)

4.1.4: We suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. (*2A*)

4.1.5: In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. (*Not Graded*)

Commentary

The increased risk of cardiovascular illness in the CKD population was highlighted in the 2002 KDOQI CKD guideline.[1] Since then, additional strong evidence has emerged in support of this relationship and several nontraditional CKD-specific risk factors for CVD have been identified.[41-43] Despite these findings, patients with CKD remain under-represented in interventional studies and as a consequence, the evidence basis for the recommendations related to cardiovascular risk reduction in CKD remains limited. Nonetheless, given the large burden of CVD in patients with CKD who have a high prevalence of traditional cardiovascular risk factors, we agree with the recommendation that risk-factor modification strategies recommended for the general population are indicated for patients with CKD. Additionally, the commentary work group believes that guideline 4.1.3 recommending antiplatelet therapy could have placed

more emphasis on aspirin (acetylsalicylic acid) as initial therapy, the agent for which there is the strongest evidence of effectiveness in patients with CKD.[44,45]

The evidence in support of CKD-specific therapeutic strategies for management of heart failure is similarly lacking. Indeed, most of the data reviewed by the guidelines for management of coronary heart disease in patients with CKD were derived from post hoc analyses of clinical trials outside of the setting of CKD.[46-49] Given that these analyses demonstrate effectiveness of these therapies in the CKD population, the guideline recommends delivery of standard heart failure treatments for patients with CKD. We support these recommendations and also agree with the recommendation that any alterations in therapy should be accompanied by close monitoring of patients' GFR and potassium levels. Finally, we believe that the guideline should have placed greater emphasis on the risk for hyperkalemia and AKI associated with dual blockade of the renin-angiotensin-aldosterone system (RAAS)[29,50-52] and recommend increased vigilance in monitoring of serum potassium and kidney function in these circumstances.

Caveats When Interpreting Tests for CVD in People With CKD

BNP/N-terminal-proBNP (NT-proBNP)

4.2.1: In people with GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of BNP/NT-proBNP be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status. (*1B*)

Troponins

4.2.2: In people with GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (*1B*)

Non-Invasive testing

4.2.3: We recommend that people with CKD presenting with chest pain should be investigated for underlying cardiac disease and other disorders according to the same local practice for people without CKD (and subsequent treatment should be initiated similarly). (*1B*)

4.2.4: We suggest that clinicians are familiar with the limitations of non-invasive cardiac tests (e.g., exercise electrocardiography [ECG], nuclear imaging, echocardiography, etc.) in adults with CKD and interpret the results accordingly. (*2B*)

Commentary

The KDIGO guideline highlights the fact that cardiac biomarkers (B-type natriuretic peptide [BNP]/N-terminal pro-BNP [NT-pro-BNP] and troponin) may be less reliable at lower levels of kidney function. These markers are inversely associated with level of GFR, suggesting that they may be filtered by the kidney and that higher levels would be derived from decreased filtration, at least in part, rather than exclusively from true cardiac damage. However, in CKD populations, BNP levels have been strongly associated with left ventricular hypertrophy and left ventricular dysfunction, even outside the setting of acute myocardial ischemia.[53-55] In addition, elevated concentrations of troponin T and troponin I by ultrasensitive assays have been associated with increased mortality.[56-58]

The commentary work group acknowledges that the preponderance of literature examining cardiac testing in the setting of kidney disease focuses only on individuals with ESRD. Nevertheless, we agree with the KDIGO's emphasis on using the same diagnostic investigation for patients with CKD presenting with possible acute coronary syndrome as used for individuals without CKD. We agree that in the clinical context of chest pain, elevations of troponins must not automatically be attributed to reduced kidney function. Since these biomarkers may be elevated in the setting of CKD in the absence of acute ischemia due to chronic left ventricular wall stress, it is important to apply clinical judgment and evaluate trends in biomarker concentrations when engaging in clinical intervention.

CKD and Peripheral Arterial Disease

4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (*2A*)

Commentary

We agree with the KDIGO guideline that peripheral arterial disease is a serious and common problem in patients with CKD. However, we do not believe there is sufficient evidence to support a strategy of routine screening of this population with ankle-brachial index. As acknowledged in the guideline, ankle-brachial index test results may have more limited value in CKD because of the high prevalence of calcified vasculature. Additionally, systematic screening has the potential to lead to adverse outcomes and increased costs as a consequence of additional testing (eg, angiography) and interventions. A more prudent approach might be to limit screening and testing to individuals with symptoms or signs of limb ischemia.

Medication Management and Patient Safety in CKD

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (*1A*)

4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (*1C*)

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. (*1C*)

4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (*1B*)

4.4.5: We recommend not using herbal remedies in people with CKD. (*1B*)

4.4.6: We recommend that metformin be continued in people with GFR $\geq$ 45 ml/min/1.73 m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m^2 (GFR category G3b); and it should be discontinued in people with GFR $<$ 30 ml/min/1.73 m^2 (GFR categories G4-G5). (*1C*)

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (*1A*)

4.4.8: People with CKD should not be denied therapies for other conditions such as cancer but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (*Not Graded*)

Commentary

Many commonly prescribed drugs or their metabolites are excreted by the kidneys and require dose adjustment to avoid potentially life-threatening complications. Furthermore, several commonly used drugs are nephrotoxic and may hasten progression of CKD or lead to AKI. Therefore, the guideline recommends drug dosing based on the level of GFR. Further, it recommends that individuals taking potentially nephrotoxic medications undergo close monitoring of their kidney function and discontinue drugs excreted by the kidneys or that are potentially nephrotoxic during periods of illness that predispose to AKI. We agree with the emphasis placed on drug dosing since this is often an under-recognized issue in the setting of CKD and has important implications for patient safety (Table 6). However, we were concerned about the recommendation to use cystatin C–based GFR estimates for drug dosing given uncertainty regarding direct effects of drugs on cystatin C generation.

The commentary work group agrees with the guideline's moderate approach to metformin dosing, which is consistent with recommendations recently published in the updated KDOQI guideline for diabetes and CKD.[30] The US Food and Drug Administration (FDA) had mandated a black-box warning for metformin that indicates it is contraindicated in patients with serum creatinine $\geq$ 1.5 mg/dL in men and $\geq$1.4 mg/dL in women based on the risk for lactic acidosis. However, some have questioned this warning and argued that it has prevented many individuals from benefitting from this drug.[59] It is now recognized that the risk for lactic acidosis in patients on metformin is extremely low, and the KDIGO guidelines reflects this new evidence.[60]

Imaging Studies

4.5.1: Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. (*Not Graded*)

Radiocontrast

4.5.2: We recommend that all people with GFR $<$ 60 ml/min/1.73 m^2 (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radio contrast media should be managed according to the *KDIGO Clinical Practice Guideline for AKI* including:

- Avoidance of high osmolar agents (*1B*);
- Use of lowest possible radio contrast dose (*Not Graded*);
- Withdrawal of potentially nephrotoxic agents before and after the procedure (*1C*);
- Adequate hydration with saline before, during, and after the procedure (*1A*);
- Measurement of GFR 48–96 hours after the procedure (*1C*).

Gadolinium-based contrast media

4.5.3: We recommend not using gadolinium-containing contrast media in people with GFR $<$15 ml/min/1.73 m^2 (GFR category G5) unless there is no alternative appropriate test. (*1B*)

4.5.4: We suggest that people with a GFR $<$ 30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadolinium containing contrast media are preferentially offered a macrocyclic chelate preparation. (*2B*)

Bowel preparation

4.5.5: We recommend not to use oral phosphate-containing bowel preparations in people with a GFR $<$ 60 ml/min/1.73 m^2 (GFR categories G3a-G5) or in those known to be at risk of phosphate nephropathy. (*1A*)

Commentary

We agree with these recommendations on the use of contrast agents in imaging studies. In particular, we also agree with the guideline recommendation to avoid gadolinium for people with GFR $<$ 15 mL/min/1.73 m^2 versus $<$30 mL/min/1.73 m^2 as is stated in the FDA's black box warning.[61] Notably, we also agree with the omission of a recommendation to not use *N*-acetylcysteine and/or sodium bicarbonate to prevent AKI caused by radio contrast media due to inconsistencies in the available evidence.

Table 6. Cautionary Notes for Prescribing in People With CKD

Agents	Cautionary notes
1. Antihypertensives/cardiac medications	
RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)	• Avoid in people with suspected functional renal artery stenosis • Start at lower dose in people with GFR < 45 ml/min/1.73 m^2 • Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation • Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery • Do not routinely discontinue in people with GFR < 30 ml/min/1.73 m^2 as they remain nephroprotective
Beta-blockers	• Reduce dose by 50% in people with GFR < 30 ml/min/1.73 m^2
Digoxin	• Reduce dose based on plasma concentrations
2. Analgesics	
NSAIDS	• Avoid in people with GFR < 30 ml/min/1.73 m^2 • Prolonged therapy is not recommended in people with GFR < 60 ml/min/1.73 m^2 • Should not be used in people taking lithium • Avoid in people taking RAAS blocking agents
Opioids	• Reduce dose when GFR < 60 ml/min/1.73 m^2 • Use with caution in people with GFR < 15 ml/min/1.73 m^2
3. Antimicrobials	
Penicillin	• Risk of crystalluria when GFR < 15 ml/min/1.73 m^2 with high doses • Neurotoxicity with benzylpenicillin when GFR < 15 ml/min/1.73 m^2 with high doses (maximum 6 g/day)
Aminoglycosides	• Reduce dose and/or increase dosage interval when GFR < 60 ml/min/1.73 m^2 • Monitor serum levels (trough and peak) • Avoid concomitant ototoxic agents such as furosemide
Macrolides	• Reduce dose by 50% when GFR < 30 ml/min/1.73 m^2
Fluoroquinolones	• Reduce dose by 50% when GFR < 15 ml/min/1.73 m^2
Tetracyclines	• Reduce dose when GFR < 45 ml/min/1.73 m^2; can exacerbate uremia
Antifungals	• Avoid amphotericin unless no alternative when GFR < 60 ml/min/1.73 m^2 • Reduce maintenance dose of fluconazole by 50% when GFR < 45 ml/min/1.73 m^2 • Reduce dose of flucytosine when GFR < 60 ml/min/1.73 m^2
4. Hypoglycemics	
Sulfonylureas	• Avoid agents that are mainly renally excreted (e.g., glyburide/ glibenclamide) • Other agents that are mainly metabolized in the liver may need reduced dose when GFR < 30 ml/min/1.73 m^2 (e.g., gliclazide, gliquidone)
Insulin	• Partly renally excreted and may need reduced dose when GFR < 30 ml/min/1.73 m^2
Metformin	• Suggest avoid when GFR < 30 ml/min/1.73 m^2, but consider risk-benefit if GFR is stable • Review use when GFR < 45 ml/min/1.73 m^2 • Probably safe when GFR ≥ 45 ml/min/1.73 m^2 • Suspend in people who become acutely unwell
5. Lipid-lowering	
Statins	• No increase in toxicity for simvastatin dosed at 20 mg per day or simvastatin 20 mg /ezetimide 10 mg combinations per day in people with GFR < 30 ml/min/1.73 m^2 or on dialysis[83] • Other trials of statins in people with GFR < 15 ml/min/1.73 m^2 or on dialysis also showed no excess toxicity
Fenofibrate	• Increases SCr by approximately 0.13 mg/dl (12 μmol/l)
6. Chemotherapeutic	
Cisplatin	• Reduce dose when GFR < 60 ml/min/1.73 m^2 • Avoid when GFR < 30 ml/min/1.73 m^2
Melphalan	• Reduce dose when GFR < 60 ml/min/1.73 m^2
Methotrexate	• Reduce dose when GFR < 60 ml/min/1.73 m^2 • Avoid if possible when GFR < 15 ml/min/1.73 m^2
7. Anticoagulants	
Low-molecular-weight heparins	• Halve the dose when GFR < 30 ml/min/1.73 m^2 • Consider switch to conventional heparin or alternatively monitor plasma anti-factor Xa in those at high risk for bleeding

(Continued)

Table 6 (Cont'd). Cautionary Notes for Prescribing in People With CKD

Agents	Cautionary notes
Warfarin	• Increased risk of bleeding when GFR < 30 ml/min/1.73 m^2 • Use lower doses and monitor closely when GFR < 30 ml/min/1.73 m^2
8. Miscellaneous	
Lithium	• Nephrotoxic and may cause renal tubular dysfunction with prolonged use even at therapeutic levels • Monitor GFR, electrolytes, and lithium levels 6 monthly or more frequently if the dose changes or the patient is acutely unwell • Avoid using concomitant NSAIDs • Maintain hydration during intercurrent illness • Risk-benefit of drug in specific situation must be weighed

Note: Data as of January 2013.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

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CKD and Risks for Infections, AKI, Hospitalizations, and Mortality

CKD and risk of infections

4.6.1: We recommend that all adults with CKD are offered annual vaccination with influenza vaccine, unless contraindicated. (*1B*)

4.6.2: We recommend that all adults with eGFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5) and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated. (*1B*)

4.6.3: We recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years. (*1B*)

4.6.4: We recommend that all adults who are at high risk of progression of CKD and have GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing. (*1B*)

4.6.5: Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies. (*Not Graded*)

4.6.6: Pediatric immunization schedules should be followed according to official international and regional recommendations for children with CKD. (*Not Graded*)

CKD and risk of AKI

4.6.7: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

4.6.7.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

CKD and risk of hospitalization and mortality

4.6.8: CKD disease management programs should be developed in order to optimize the community management of people with CKD and reduce the risk of hospital admission. (*Not Graded*)

4.6.9: Interventions to reduce hospitalization and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and cardiovascular disease in particular. (*Not Graded*)

Commentary

We agree with the guideline that the benefits of immunization are far greater than the associated risks. If there are no contraindications, patients with CKD should receive the influenza vaccine annually and the pneumococcal vaccine with a booster vaccination every 5 years.[62] Newer vaccines recommended for the general population should also be administered to patients with CKD. As emphasized in the guideline, while the recommendations for hepatitis B vaccine are limited to patients with CKD who may undergo renal replacement therapy (RRT), all patients with CKD may benefit from vaccination if they have not been previously immunized or developed natural immunity from prior hepatitis B infection.

Compared to the original KDOQI CKD guideline, these KDIGO recommendations devote greater attention to the risk of AKI in patients with CKD and refer to the KDIGO AKI guideline for more specific recommendations.[63] This strong emphasis is a byproduct of the emergence of the large body of literature on AKI in CKD since the publication of the KDOQI CKD guidelines. The commentary work group agrees with this position.

Given insufficient data on specific causal mechanisms for the observed associations between CKD and risks of hospitalization and mortality, the guideline does not identify targeted interventions. Instead, a comprehensive approach to care for multiple comorbid conditions, especially CVD, is appropriately promoted as best clinical practice. The commentary work group agrees with this approach.

Implementation

1. The risks of complications of CKD, such as CVD, infections, AKI, and others discussed in this chapter, may be less well known to non-nephrologist providers. For example, in the case of CVD, educational efforts should be focused on primary care providers, emergency medicine physicians, nephrologists, and cardiologists. Education on immunizations in patients with CKD should focus mainly on primary care physicians, who are most likely to implement routine vaccinations.

2. Management of the increased cardiovascular risk will require coordination of care among providers. This issue is more fully explored in chapter 5 of the KDIGO guideline. For example, the need for additional peripheral arterial disease evaluation and interventions will require involvement of radiologists and vascular surgeons. Primary care providers will likely take on primary responsibility for managing CVD risk in patients with CKD, whereas nephrologists will often maintain a narrower focus on management of specific CKD-related issues (eg, resistant hypertension, mineral and bone disorders, and anemia).

3. Implementation will require the further development of electronic medical record systems to provide real-time alerts and guidance in drug dosing for patients with CKD. Reporting of eGFR in units of mL/min will also facilitate appropriate drug dosage adjustment by all providers and health care professionals.

4. Pharmacovigilance systems may also facilitate prevention of unsafe exposure to contrast agents and to oral phosphate-containing bowel preparations in individuals with GFR < 60 mL/min/1.73 m^2.

REFERRAL TO SPECIALISTS AND MODELS OF CARE

Referral to Specialist Services

5.1.1: We recommend referral to specialist kidney care services for people with CKD in the following circumstances (*1B*):
- AKI or abrupt sustained fall in GFR;
- GFR $<$ 30 ml/min/1.73 m^2 (GFR categories G4-G5)*;
- a consistent finding of significant albuminuria (ACR $\geq$ 300 mg/g [$\geq$ 30 mg/mmol] or AER $\geq$ 300 mg/24 hours, approximately equivalent to PCR $\geq$ 500 mg/g [$\geq$50 mg/mmol] or PER $\geq$ 500 mg/24 hours);
- progression of CKD (see Recommendation 2.1.3 for definition);
- urinary red cell casts, RBC $>$20 per high power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;
- persistent abnormalities of serum potassium;
- recurrent or extensive nephrolithiasis;
- hereditary kidney disease.

5.1.2: We recommend timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10-20% or higher†, as determined by validated risk prediction tools. (*1B*)

*If this is a stable isolated finding, formal referral (i.e., formal consultation and ongoing care management) may not be necessary and advice from specialist services may be all that is required to facilitate best care for the patients. This will be health-care system dependent.

†The aim is to avoid late referral, defined here as referral to specialist services less than 1 year before start of RRT.

Commentary

Both of these recommendations were level 1 grade recommendations. These are common sense, clear, and actionable recommendations that should be straightforward for the primary care physician to implement. We agree that consideration of both GFR and albuminuria will guide appropriate referrals, thereby reducing problems of under-referral and late referral to nephrologists. We also agree that referral of all patients with CKD stage 4 or worse will promote interventions to delay progression and reduce CKD complications, as well as the ability to prepare for RRT. In contrast, the commentary work group questioned the appropriateness of referring all patients with ACR $>$ 300 mg/g. Rather, the commentary work group thought that the decision to refer should be tailored to the specific needs of the patient and the provider's capacity to deliver specialty care. In the opinion of the commentary work group, 2 groups of patients who should be referred are those with side effects or contraindications to ACE-inhibitor/ARB therapy, but albuminuria $>$ 300 mg/g or nephrotic-range albuminuria or proteinuria. We suggest modifying the list above to add:

- *Questions about the etiology of albuminuria.*
- *Difficulty with decreasing level of albuminuria despite institution of ACE-inhibitor or ARB therapy.*

We believe the recommendations to use validated prediction models for the development of kidney failure to guide timely referral for RRT is appropriate. The commentary work group notes that the current available prediction models are based on observational studies of patients in nephrology clinics who progressed to ESRD in non-US populations.[2] Prior to their widespread use, these or other models should be validated in other cohorts that are generalizable to the US population with CKD. Among certain subgroups of patients, the risk of death is higher than the risk of ESRD.[64,65] If planning for RRT is not properly targeted to patients with a high enough risk of ESRD, then the costs and/or harms of this care might outstrip the benefits.

Care of the Patient With Progressive CKD

5.2.1: We suggest that people with progressive CKD should be managed in a multidisciplinary care setting. (*2B*)

5.2.2: The multidisciplinary team should include or have access to dietary counseling, education and counseling about different RRT modalities, transplant options, vascular access surgery, and ethical, psychological, and social care. (*Not Graded*)

Commentary

KDIGO recommendations regarding the care of patients with progressive CKD are not based on strong evidence, but we believe that they are sensible and rooted in existing models of care for individuals with other chronic diseases.

Timing the Initiation of RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2. (*2B*)

5.3.2: Living donor preemptive renal transplantation in adults should be considered when the GFR is $<$20 ml/min/1.73 m^2, and there is evidence of progressive and irreversible CKD over the preceding 6-12 months. (*Not Graded*)

Commentary

The commentary work group agrees with KDIGO that dialysis initiation, for both peritoneal dialysis and hemodialysis, should not be based on estimates of kidney function alone, but should take into account symptoms and other complications of advancing kidney disease. We further recommend that the interpretation of symptoms be individualized with consideration of the expected benefit each patient may derive from starting dialysis.

Structure and Process of Comprehensive Conservative Management

5.4.1: Conservative management should be an option in people who choose not to pursue RRT and this should be supported by a comprehensive management program. *(Not Graded)*

5.4.2: All CKD programs and care providers should be able to deliver advance care planning for people with a recognized need for end-of-life care, including those people undergoing conservative kidney care. (*Not Graded*)

5.4.3: Coordinated end-of-life care should be available to people and families through either primary care or specialist care as local circumstances dictate. (*Not Graded*)

5.4.4: The comprehensive conservative management program should include protocols for symptom and pain management, psychological care, spiritual care, and culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting), followed by the provision of culturally appropriate bereavement support. (*Not Graded*)

Commentary

The KDIGO guideline presents 4 ungraded recommendations regarding the details of comprehensive conservative management. We agree with the goals of these recommendations, noting their consistency with practice guidelines on shared decision making from the Renal Physician's Association and the American Board of Internal Medicine/American Society of Nephrology "Choosing Wisely" campaign.[66,67] However, these recommendations may be difficult to implement in the United States due to uneven access to palliative care across health care systems, a shortage of palliative-care physicians, limited training of US nephrologists in these areas, and poor reimbursement for these and other cognitive services.

Implementation

1. Agreement for the coordination of referral to nephrologists and joint clinical management by primary care physicians, nephrologists, and other specialists should follow the principles of the patient-centered medical home, which is a paradigm whereby the relationships and communication among providers are specified and mechanisms exist for regular review of the agreement's effectiveness. Payment systems should promote this coordination of care by, for example, reimbursing for electronic or telephone communication among providers.

2. The elements of multidisciplinary care teams are present in many, but not all US health care systems and some payers may not reimburse for the services provided by nonphysician team members. For eligible patients with an eGFR of 15-29 mL/min/1.73 m^2, CKD education services are reimbursable through the Kidney Disease Education Benefit of the Medicare Improvements for Patients and Providers Act of 2008. However, this is not accessible to all patients due to copays and inconsistent implementation of education services across US nephrology practices.

3. With respect to the timing of dialysis initiation, a strategy of "watchful waiting" until the appearance of uremic symptoms represents a significant shift in US practice and has potential to result in significant cost savings for the health care system. Parity in the payment structure for dialysis management and advanced CKD management could facilitate redeployment of resources to safely manage patients in advanced CKD clinics.

4. Many US nephrology practices and health care systems are not equipped to incorporate recommendations concerning conservative management of advanced CKD into clinical practice. To facilitate the implementation of these recommendations, professional societies and accreditation organizations should emphasize training in palliative care for all nephrology providers. Payment reforms for palliative care services and adoption of quality metrics for palliative CKD care should also provide incentives to manage patients with advanced CKD who elect not to receive RRT.[68]

CONCLUSION

The KDIGO guideline recommendations on evaluation and management of CKD serve as an excellent summary of the state our knowledge and available evidence on CKD. Importantly, they provide an important and needed update to the staging system based on newly available data. They also highlight gaps in knowledge to guide future investigative efforts.

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REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(suppl 2):S1-S266.

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

3. Levey AS. A decade after the KDOQI CKD guidelines. *Am J Kidney Dis*. 2012;60:683-685.

4. Kasiske BL, Eckardt KU. Evidence and outcomes in CKD. *Am J Kidney Dis*. 2012;59:492-494.

5. Kidney Disease: Improving Global Outcomes (KDIGO). About us. http://kdigo.org/home/about-us/. Accessed November 26, 2013.

6. Levey AS, de Jong PE, Coresh J, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80:17-28.

7. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073-2081.

8. Van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341-1352.

9. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79:1331-1340.

10. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80:93-104.

11. Moyer VA; U.S. Preventive Services Task Force. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:567-570.

12. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-1252.

13. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36(suppl 1):S11-S66.

14. National Kidney Disease Education Program (NKDEP). Creatinine Standardization. http://nkdep.nih.gov/lab-evaluation/gfr/creatinine-standardization.shtml. Accessed November 6, 2013.

15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.

16. Andersen TB, Jødal L, Boegsted M, et al. GFR prediction from cystatin C and creatinine in children: effect of including body cell mass. *Am J Kidney Dis*. 2012;59:50-57.

17. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20-29.

18. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012;157:471-481.

19. Teo BW, Xu H, Koh YY, et al. Estimating kidney function in a multiethnic Asian population with multiple filtration markers. *Am J Kidney Dis*. 2012;60:500-502.

20. Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932-943.

21. Lieske JC, Bondar O, Miller WG, et al. A reference system for urinary albumin: current status. *Clin Chem Lab Med*. 2013;51:981-989.

22. Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol*. 2009;10:30.

23. Turin TC, Coresh J, Tonelli M, et al. One-year change in kidney function is associated with an increased mortality risk. *Am J Nephrol*. 2012;36:41-49.

24. Turin TC, Coresh J, Tonelli M, et al. Short-term change in kidney function and risk of end-stage renal disease. *Nephrol Dial Transplant*. 2012;27:3835-3843.

25. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl*. 2009;76:337-414.

26. National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(suppl 1):S1-S290.

27. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8) [published online ahead of print December 18, 2013]. *JAMA*.

28. Systolic Blood Pressure Intervention Trial (SPRINT). Justification for CKD subgroup. https://www.sprinttrial.org/public/dspSprintScience.cfm. Accessed November 27, 2013.

29. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369:1892-1903.

30. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60:850-886.

31. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.

32. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129-139.

33. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.

34. Kwan BC, Murtaugh MA, Beddhu S. Associations of body size with metabolic syndrome and mortality in moderate chronic kidney disease. *Clin J Am Soc Nephrol*. 2007;2:992-998.

35. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. *Am J Kidney Dis*. 2007;49:581-591.

36. Ricardo AC, Madero M, Yang W, et al. Adherence to a healthy lifestyle and all-cause mortality in CKD. *Clin J Am Soc Nephrol*. 2013;8:602-609.

37. Dumler F, Kilates C. Prospective nutritional surveillance using bioelectrical impedance in chronic kidney disease patients. *J Ren Nutr*. 2005;15:148-151.

38. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279-335.

39. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009;76:S1-S130.

40. Institute of Medicine (IOM). Sodium intake in populations: assessment of evidence, 2013 report. http://iom.edu/Reports/2013/Sodium-Intake-in-Populations-Assessment-of-Evidence/Report-Brief051413.aspx. Accessed January 7, 2014.

41. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol*. 2007;50:217-224.

42. Menon V, Greene T, Wang X, et al. C-Reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int*. 2005;68:766-772.

43. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. 2011;121:4393-4408.

44. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol*. 2010;56:956-965.

45. Best PJ, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. *Am Heart J*. 2008;155:687-693.

46. Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J*. 2008;155:791-805.

47. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation*. 2009;120:1577-1584.

48. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation*. 2006;113:671-678.

49. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail*. 2001;3:469-479.

50. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547-553.

51. Lakhdar R, Al-Mallah MH, Lanfear DE. Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. *J Card Fail*. 2008;14:181-188.

52. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543-551.

53. Mishra RK, Li Y, Ricardo AC, et al. Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol*. 2013;111:432-438.

54. Tagore R, Ling LH, Yang H, Daw HY, Chan YH, Sethi SK. Natriuretic peptides in chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1644-1651.

55. Takami Y, Horio T, Iwashima Y, et al. Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. *Am J Kidney Dis*. 2004;44:420-428.

56. Abbas NA, John RI, Webb MC, et al. Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. *Clin Chem*. 2005;51:2059-2066.

57. Wood GN, Keevil B, Gupta J, et al. Serum troponin T measurement in patients with chronic renal impairment predicts survival and vascular disease: a 2 year prospective study. *Nephrol Dial Transplant*. 2003;18:1610-1615.

58. Lamb EJ, Kenny C, Abbas NA, et al. Cardiac troponin I concentration is commonly increased in nondialysis patients with

CKD: experience with a sensitive assay. *Am J Kidney Dis*. 2007;49:507-516.

59. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care*. 2011;34:1431-1437.

60. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;4:CD002967.

61. US Food and Drug Administration. FDA Drug Safety Communication (2010): new warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm. Accessed January 7, 2014.

62. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Am J Transplant*. 2013;13:232-235.

63. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int*. 2012;2:1-138.

64. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18:2758-2765.

65. Dalrymple LS, Katz R, Kestenbaum B, et al. Chronic kidney disease and the risk of end-stage renal disease versus death. *J Gen Intern Med*. 2011;26:379-385.

66. Moss AH. Revised dialysis clinical practice guideline promotes more informed decision-making. *Clin J Am Soc Nephrol*. 2010;5:2380-2383.

67. Williams AW, Dwyer AC, Eddy AA, et al. Critical and honest conversations: the evidence behind the "Choosing Wisely" campaign recommendations by the American Society of Nephrology. *Clin J Am Soc Nephrol*. 2012;7:1664-1672.

68. Tamura MK, Meier DE. Five policies to promote palliative care for patients with ESRD. *Clin J Am Soc Nephrol*. 2013;8:1783-1790.

69. Carter JL, Tomson CR, Stevens PE, et al. Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrol Dial Transplant*. 2006;21:3031-3037.

70. Heathcote KL, Wilson MP, Quest DW, et al. Prevalence and duration of exercise induced albuminuria in healthy people. *Clin Invest Med*. 2009;32:E261-E265.

71. Vehaskari VM. Orthostatic proteinuria. *Arch Dis Child*. 1982;57:729-730.

72. Leung AK, Wong AH. Proteinuria in children. *Am Fam Physician*. 2010;82:645-651.

73. Howey JE, Browning MC, Fraser CG. Selecting the optimum specimen for assessing slight albuminuria, and a strategy for clinical investigation: novel uses of data on biological variation. *Clin Chem*. 1987;33:2034-2038.

74. Boger CA, Chen MH, Tin A, et al. CUBN is a gene locus for albuminuria. *J Am Soc Nephrol*. 2011;22:555-570.

75. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? *Ann Clin Biochem*. 2009;46:205-217.

76. Miller WG. Urine albumin: recommendations for standardization. *Scand J Clin Lab Invest Suppl*. 2008;241:71-72.

77. Levey AS, Gassman JJ, Hall PM, et al. Assessing the progression of renal disease in clinical studies: effects of duration of follow-up and regression to the mean. Modification of Diet in Renal Disease (MDRD) Study Group. *J Am Soc Nephrol*. 1991;1:1087-1094.

78. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330:877-884.

79. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-2431.

80. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int*. 2006;69:375-382.

81. Jones C, Roderick P, Harris S, et al. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. *Nephrol Dial Transplant*. 2006;21:2133-2143.

82. Levin A, Djurdjev O, Beaulieu M, et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis*. 2008;52:661-671.

83. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet*. 2011;377:2181-2192.