Canadian Society of Nephrology Commentary on the KDIGO Clinical Practice Guideline for CKD Evaluation and Management

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We congratulate the KDIGO (Kidney Disease: Improving Global Outcomes) work group on their comprehensive work in a broad subject area and agreed with many of the recommendations in their clinical practice guideline on the evaluation and management of chronic kidney disease. We concur with the KDIGO definitions and classification of kidney disease and welcome the addition of albuminuria categories at all levels of glomerular filtration rate (GFR), the terminology of G categories rather than stages to describe level of GFR, the division of former stage 3 into new G categories 3a and 3b, and the addition of the underlying diagnosis. We agree with the use of the heat map to illustrate the relative contributions of low GFR and albuminuria to cardiovascular and renal risk, though we thought that the highest risk category was too broad, including as it does people at disparate levels of risk. We add an albuminuria category A4 for nephrotic-range proteinuria and D and T categories for patients on dialysis or with a functioning renal transplant. We recommend target blood pressure of 140/90 mm Hg regardless of diabetes or proteinuria, and against the combination of angiotensin receptor blockers with angiotensin-converting enzyme inhibitors. We recommend against routine protein restriction. We concur on individualization of hemoglobin A1c targets. We do not agree with routine restriction of sodium intake to <2 g/d, instead suggesting reduction of sodium intake in those with high intake (>/=3.3 g/d). We suggest screening for anemia only when GFR is <30 mL/min/1.73 m2. We recognize the absence of evidence on appropriate phosphate targets and methods of achieving them and do not agree with suggestions in this area. In drug dosing, we agree with the recommendation of using absolute clearance (ie, milliliters per minute), calculated from the patient’s estimated GFR (which is normalized to 1.73 m2) and the patient’s actual anthropomorphic body surface area. We agree with referral to a nephrologist when GFR is <30 mL/min/1.73 m2 (and for many other scenarios), but suggest urine albumin-creatinine ratio >/=60 mg/mmol or proteinuria with protein excretion >/=1 g/d as the referral threshold for proteinuria.

INDEX WORDS: Estimated glomerular filtration rate (eGFR); chronic kidney disease (CKD) staging; albuminuria; kidney disease progression; Kidney Disease: Improving Global Outcomes (KDIGO); clinical practice guideline; Canadian Society of Nephrology (CSN).

The KDIGO (Kidney Disease: Improving Global Outcomes) guideline on chronic kidney disease (CKD)1 represents an extraordinary effort of evidence summary and synthesis, together with thoughtful expression of best practices and opinion. Because Canada is a large country with universal health care and good primary care structure, some recommendations by the international guidelines groups might not be relevant to the Canadian population; we aim to review the evidence behind recommendations, note points of disagreement, and place issues in context for Canadian clinicians.

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Originally published online December 12, 2014.

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http://dx.doi.org/10.1053/j.ajkd.2014.10.013


METHODS

The commentary committee co-chairs selected potential members from their knowledge of the Canadian kidney community, aiming to represent people from the whole range of relevant disciplines, from academic and community centers, and from across Canada. Some committee members were identified through snowball methodology from other experts, and others were identified through internet searches of academic departments.

Once the commentary committee was determined, we used the general methodology of other CSN (Canadian Society of Nephrology) guidelines, and in keeping with other commentaries, divided our comments into those that we thought might interest anyone in the international community of those who care for people with CKD and those that were specifically directed at the Canadian context.

Each committee member first provided comments on the whole document, which were collated and circulated. Though different people highlighted different issues, there was general concordance at this stage. Using this material, pairs of writers selected for their expertise in the area wrote the first draft of the commentary and received feedback from a different pair and from the co-chairs. Subsequent drafts received feedback from all committee members. We used teleconferences selectively to set up our plan of work and discuss differences of opinion that arose during drafting. Our process and decisions have been documented.

We considered our readership to be people like ourselves: health care workers in primary, secondary, or tertiary care who look after patients with kidney disease, recognizing that some of the issues are somewhat specialized and less relevant at the level of primary care. We were explicitly primarily interested in interventions that affect patient-important, rather than surrogate, outcomes. We attempted to make our recommendations clear and actionable. We accepted that there were situations in which alternative courses of action would be reasonable practice.

We attempted to produce suggestions and recommendations that were in keeping with or at least recognized the importance of our understanding of the values and preferences of Canadians, along with addressing resource and feasibility questions that are specifically Canadian. Overall, our philosophy and processes have been aligned with the suggestions of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

We noted that it was sometimes difficult to understand the rationale for the level-of-evidence gradings (see Item S1 [available as online supplementary material] for examples); however, we recognized that producing a consistent and evidence-based recommendation for a large number of statements is an enormous and difficult task. We have not attempted to address this issue systematically. The material we have quoted from the original KDIGO guideline reproduces the original gradings, which we have not modified and do not always agree with.

When we disagreed with the substance of the KDIGO recommendation, we have indicated that and discussed the reasons for our disagreement in the commentary.

Screening. One important point that was beyond the scope of the KDIGO CKD guideline, but which often arose in our discussion, was the identification of people with CKD. Screening studies have shown very large numbers needed to screen to identify a person with progressive kidney disease. In the early stages of disease, the evidence for differential intervention (ie, using different treatments based on the knowledge of the kidney disease) is not strong. Because of these factors, along with the economic considerations and the potential for adverse personal and insurance consequences from labeling, we are not advocating any form of screening at present. Practitioners should continue to use case finding in keeping with usual clinical practice: in people with new-onset or long-standing hypertension or diabetes, people with vascular disease, people who are to undergo major surgery or be exposed to other potential causes of acute kidney injury (AKI), people with multisystem or generalized symptoms, people who are being considered for nephotoxic medications or medications that require dose adjustment for renal function, people with a family history of polycystic kidney disease or hereditary nephritis, and people from First Nations populations or other ethnic groups known to be at increased risk. In many of these cases, it is glomerular filtration rate (GFR) that is most relevant and that may be the initial measurement. In people with diabetes, urine albumin measurement is widely used for case finding. Either initially or in people identified with low GFR, it may be clinically appropriate to measure proteinuria, either as albumin-creatinine ratio (ACR), protein-creatinine ratio (PCR), or dipstick. We recognize that there is substantial within-individual day-to-day variation in proteinuria, but do not think that it is appropriate to recommend multiple measurements as an initial approach (as tends to occur in people with diabetes). Though multiple measurements inevitably have better measurement properties than single measurements, most of the evidence for the risk associated with low GFR and proteinuria in general populations has been based on single measurements, and routinely implementing multiple measurements greatly increases costs and complexity. In terms of follow-up measurements, we recognize that even less is known.
about appropriate intervals for rescreening. For people identified as having kidney disease, remeasurement should be based on the severity of the abnormality found, previous values, and the clinical context. For those without kidney disease, appropriate intervals for remeasurement might be measured in years or, in some cases, decades.

We know that many agencies are working on actionable algorithms for approach to the detection of kidney disease in high-risk groups, guided by evidence, opinion, and best practices and motivated by the desire to prevent progression at early stages, when the impact of reduction will be greatest. Studies of the impact of these strategies will inform further recommendations and, we hope, interventional studies in the area.

The structure of this commentary aligns with the structure of the KDIGO guideline. 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 committee, comments on key guideline recommendations and discusses special implications for Canada.

### 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

We agree that CKD should be defined as the presence of important kidney damage or decreased kidney function for 3 or more months. A key criticism of this conceptual definition in the literature is that the parameters used in defining CKD, such as asymptomatic low GFR, albuminuria, and other asymptomatic urinary abnormalities, are biomarkers, but not disease entities. However, these biomarkers are associated with increased risk of adverse clinical outcomes (end-stage renal disease [ESRD], cardiovascular disease, and mortality) in community-dwelling patients in the community and in nephrology practices and should be considered within their overall care. Some have recommended that people in GFR category G3a without associated markers of kidney damage (albuminuria or hematuria) should not necessarily be considered to have CKD and should be considered for further evaluation and referral according to the clinical judgment of the health care provider. Labeling people as having CKD has important implications, including insurance problems. We recommend that in patients with estimated GFR (eGFR) < 60 ml/min/1.73 m², urine protein assessment (ACR, PCR, or a dipstick) and a repeat measurement of kidney function be undertaken. If the low GFR is likely long term, the repeat assessment could be in 3 months, which would satisfy criteria for CKD. However, if low GFR could be acute or subacute, the repeat assessment should be made sooner, sometimes within days, depending on the clinical situation, so

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥ 90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mildly decreased*</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

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. Reproduced with permission of KDIGO from.
that AKI can be recognized and further investigation and treatment can proceed without delay.

**Implications Within Canadian Health Care**

The current operational definition for CKD is a useful and pragmatic concept for practice, research, and policy formulation. It provides a common language for communication among health care providers, patients and their families, investigators, and policy makers, at the risk of labeling effects and insurability issues for some Canadians. It has important implications for public health and clinical practice as it provides a framework for identifying patients at risk of adverse outcomes (ESRD, cardiovascular risk, and mortality) that does not always require specialist consultation. Further, the framework also creates a potential for reliable estimates of the burden of CKD as hitherto, nationwide data on CKD were available only for renal replacement therapy (RRT) recorded through the Canadian Organ Replacement Registry.

**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)*

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (mg/mmol)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>&lt;3</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>Moderately increased*</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>&gt;30</td>
<td>Severely increased**</td>
</tr>
</tbody>
</table>

1.2.4: Assign albuminuria* categories as follows *(Not Graded)*

*note that where albuminuria measurement is not available, urine reagent strip results can be substituted.

**Commentary**

The new classification based on cause (C category), GFR (G category), and albuminuria (A category) improves construct validity (the ability of the classification to describe important aspects of CKD) at the expense of greater complexity, a worthwhile tradeoff for nephrologists caring for patients as it is always possible to collapse and simplify it as needed. **We suggest that an additional A4 category for nephrotic-range proteinuria be added** (albumin excretion rate > 2,220 mg/d [i.e., ACR > 2,220 mg/g or 220 mg/mmol]). This cut point is widely used in differential diagnosis, with patients with nephrotic-range proteinuria having a high likelihood of glomerular disease, and has been long used in research to define particularly high-risk groups for study. In the previous staging system, CKD in patients on dialysis received subclassification as GFR stage 5D to highlight the specialized care that they require, but this has now been omitted and aggregated as G5 (GFR < 15 mL/min/1.73 m²). Distinguishing patients on dialysis from those who are not is critical and we recommend that the D designation continue to be used; similarly, a T designation should continue to be used for recipients of functioning kidney transplants. Failure to make these distinctions risks extrapolation of treatments and prognosis between patients with CKD but not ESRD and those on dialysis and with transplants. Finally, the addition of cause to the classification system highlights the difficulties of managing CKD in primary care (where most patients with CKD receive care): clinical judgment is required to determine how likely the problem is due to vascular disease, hypertension, or diabetes; the leading causes; or whether further evaluation for alternative, possibly treatable, diagnoses is needed. Overall, this classification, like the one it replaces, is valuable to administration, clinicians, educators, and researchers in generating a standardized stratification.

**Using Predicted Risk to Guide Testing and Treatment Decisions**

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)*

**Commentary**

With respect to recommendation 1.3.1, we discuss risk prediction models in the commentary on
guideline recommendation 2.1.1. We concur with recommendation 1.3.2.

Using a Heat Map to Understand the Association of Low GFR and Proteinuria With Risk

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”]

Commentary

With the new guideline recommendations, patients with CKD can now be risk stratified into 18 separate categories based on GFR and albuminuria categories. Outside decision support software, this is rather complex for clinical application, especially in primary care. The key message is that cardiovascular and renal risk increase with lower GFR and higher albuminuria or proteinuria, and that the increase in risk is at least additive. The heat map is helpful in illustrating this. We suppose that the choice of risk category boundaries (where the color changes) was informed by the desire to facilitate primary care decision making; however, because the classification system will be used in many other contexts, we did not concur that the highest risk category should include such a broad range of risk. Those within the red category with highest proteinuria and lowest GFR carry risks that are quantitatively different from those at the borders and should be distinguished in the heat map. Clinical judgment, guided by a few key principles, will continue to determine who to refer.

Evaluation of CKD Chronicity and Cause

1.4.1: Evaluation of chronicity
1.4.1.1: In people with GFR < 60 ml/min/1.73 m² (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)

Commentary

We concur with guideline recommendations 1.4.1.1 and 1.4.2.1.

Use of Serum Creatinine and Cystatin C in Estimating 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 (eGFRcrea) rather
than relying on the serum creatinine concentration alone.
- understand clinical settings in which eGFRcreat is less accurate.

Commentary
We concur with recommendations 1.4.3.1 and 1.4.3.3. With respect to recommendation 1.4.3.2, a number of low-molecular-weight serum proteins, such as β2-microglobulin, retinol-binding protein, and cystatin C, are proposed as suitable alternative endogenous filtration markers. Of these, cystatin C has received the most interest in the published literature. Several studies have compared the accuracy of serum cystatin C and creatinine in relation to a reference standard of GFR, most finding the measurement properties of serum cystatin C to be similar to or better than those of serum creatinine. However, some studies have potential weaknesses, including lack of assay standardization, inadequate sample sizes, selection of an inappropriate reference standard for GFR, variable choice of GFR cutoff level discriminating normal from impaired kidney function, lack of standardization of GFR to body surface area, and uncertain generalizability of data. In addition, validated information on cystatin C performance properties as a GFR surrogate in infants, children, adolescents, and young adults with CKD is currently lacking. However, the biggest issue is lack of evidence of effectiveness (are outcomes improved by more accurate risk stratification?) and cost-effectiveness. We do not recommend the widespread use of cystatin C in clinical practice.

Implications Within Canadian Health Care
With respect to recommendation 1.4.3.2, although cystatin C reference ranges have been reported, there is no standard reference for calibration of measurements across laboratories in Canada (work is in progress) and availability is limited to reference laboratories at present. We do not consider this problematic as its effectiveness has yet to be demonstrated.

Reporting of eGFR
1.4.3.4: We recommend that clinical laboratories should (18):
- 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 eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat.
- report eGFRcreat 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).
  - We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m² in adults using the units ml/min/1.73 m².
  - We recommend eGFRcreat levels less than 60 ml/min/1.73 m² should be reported as “decreased.”

Commentary
GFR is influenced by physiologic stressors such as acute illness, vasodilation (eg, sunburns), hydration status, vigorous activity, hormonal influences (puberty, pregnancy, menopause, and andropause), and medications. These caveats must be taken into account in interpreting reported eGFR. Furthermore, inpatients may not be, and people with subacute or acute kidney injury are not, in steady state. However, reporting has raised awareness of CKD and has uses in clinical practice and administration, as well as in research.

Pediatric considerations. We suggest that in younger children, measured GFR evaluations be delayed at least 2 weeks after any intercurrent illnesses (opinion). This is especially relevant when GFR is being used to make the decision for preemptive renal transplant listing.

Implications Within Canadian Health Care
No study has demonstrated improved patient-important outcomes with routine laboratory reporting of eGFR. Implementation of eGFR has been widely studied in Canada and been found to be associated with a 2% increase in prescription of renin-angiotensin system (RAS) blockade to people with low GFRs; no reduction in inappropriate dosing of antibiotics in people with CKD; an increase in referrals, workload, and waiting times to see a nephrologist; an increase in the number of referrals of people with eGFRs < 30 mL/min/1.73 m² in one study and no change in another; an increase in the total number of appropriate referrals, but no change in the proportion of appropriate referrals; an increase in the proportion of women and elderly people referred; and no change in eGFR at initiation of dialysis. In Australia, the proportion of late referrals decreased slightly (from 24% to 20%) with the initiation of eGFR reporting: there were more marked effects for First Nations peoples and a decrease in late referral for older patients, but an increase in late
referral for younger patients. Rightly or wrongly, routine eGFR reporting is a fait accompli, and we acknowledge this by using eGFR throughout in our recommendations.

Calibration of serum creatinine to the gold standard of isotope-dilution mass spectrometry is an essential prerequisite to the use of any formula to estimate GFR. To estimate GFR, either the MDRD (Modification of Diet in Renal Disease) Study equation or the CKD-EPI (CKD Epidemiology Collaboration) equation may be used. We recommend the use of the latter because of its better accuracy, particularly at high GFRs; validity (ability to discriminate between individuals at different risks); and calibration (ability to accurately predict the magnitude of risk). There is little difference in ease of implementation: both require the input of a variable for ethnicity (black vs nonblack) that is not usually available at a laboratory level, but that can be incorporated by treating physicians during interpretation. Either can be used in patients with transplants. Though these are the most accurate methods available to clinical practice and represent improvements over measured creatinine clearance by 24-hour collection, knowing that their accuracy is limited (in 16%-20% of people with eGFR < 60 mL/min/1.73 m², the true value differs from the reported estimate by >30% of the reported estimate) is critical to understanding the meaning of estimates and optimizing the use of estimating equations in clinical practice.

### Use of Cystatin C and Measured GFR

#### 1.4.3.5: We suggest measuring cystatin C in adults with eGFRcreat 45–59 ml/min/1.73 m² who do not have markers of kidney damage if confirmation of CKD is required. (2C)
- If eGFRcys/eGFRcreat-cys is also <60 ml/min/1.73 m², the diagnosis of CKD is 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 eGFRcys and eGFRcreat-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 eGFRcys and eGFRcreat-cys.
- report eGFRcys and eGFRcreat-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).
  - We recommend that eGFRcys and eGFRcreat-cys be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m² in adults using the units ml/min/1.73 m².
  - We recommend reporting eGFRcys and eGFRcreat-cys levels less than 60 ml/min/1.73 m² 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

We disagree that measuring cystatin C has a place in routine clinical practice (recommendations 1.4.3.5 through 1.4.3.7; see the comments on guideline statement 1.4.3.2). We concur with recommendation 1.4.3.8.

### 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 Graded):
- 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., \(z_1\)-microglobulin, monoclonal heavy or light chains, [known in some countries as “Bence Jones” proteins]). (Not Graded)

Commentary

Urinary protein excretion has important prognostic implications not only for CKD progression, but also for risk of other adverse clinical outcomes, including all-cause mortality and cardiovascular events, irrespective of baseline kidney function.¹⁰,¹¹ The KDIGO CKD guideline recommends using ACR, with suggestions for alternative measures based on available resources for different settings across the world. In CKD other than diabetic nephropathy, proteinuria may be a better marker of glomerular damage and risk of CKD progression, particularly in the range of protein excretion > 1 g/d. Most previous research in renal populations has used proteinuria as a measure of risk. The choice of ACR over PCR and the other semiquantitative measures was not based on their relative abilities to quantify urine protein excretion, but a better precision of ACR measurements particularly at lower levels of protein excretion in the urine.¹² The value of repeat, confirmatory, and complementary measurements of proteinuria (recommendation 1.4.4.3) has not been shown. If a monoclonal gammopathy is suspected (1.4.4.4), serum and urine protein electrophoresis should be performed.

Implications Within Canadian Health Care

For assessment of urine protein, we are concerned that exclusive application of the ACR measure across the country may have significant resource implications considering the differential cost of the various tests (eg, in Alberta, direct costs are $0.50 for reagent strip, $1.00 for PCR, and $2.00 for ACR; G. Cembrowski, MD, PhD [Director, Medical Biochemistry, University of Alberta Hospital], personal communication, September 2014), though this will vary by region and change over time. However, we recognize the need to develop local clinically sensible algorithms for risk stratification and diagnosis that incorporate a standardized approach, in which case, though each of the 3 measures has disadvantages, we consider each of them appropriate.

DEFINITION, IDENTIFICATION, AND PREDICTION OF CKD PROGRESSION

Recognition of CKD in Canada occurs through case finding, as the evidence for screening is not strong and is not recommended as part of our periodic health examination.⁴⁰ The difference in rates of progression of kidney diseases for patients in primary care and those seen by nephrologists is a testament to appropriate referral and retention patterns by both sets of practitioners. The recognition and referral to nephrologists of unusual, unexplained, progressive, or severe manifestations of kidney disease is a complex task requiring knowledge and experience, which this KDIGO guideline and our commentary will supplement rather than replace.

Frequency of eGFR and Albuminuria Measurements

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)

Commentary

Most people with low GFRs are followed up in primary care or by other specialists rather than nephrologists.⁴¹ In unscreened nondiabetic people with low GFRs who are not followed up in nephrology practices, the average rate of change of kidney function is 0.05 to 1.5 mL/min per year,⁴¹,⁴² which does not differ greatly from expected age-related decline.⁴³ People with diabetes and African Americans with hypertension experience rates of loss of 2.0 to 2.7 mL/min per year.⁴⁴,⁴⁵ However, patients referred to nephrologists experience rates of decline of 2.7 to 4.9 mL/min per year.⁴⁶-⁴⁸ There is no evidence that frequent monitoring of low GFR and albuminuria in the community improves outcomes, and it is difficult to translate the slow average rates of progression into a prescription for frequency of monitoring. Furthermore, though decreases in albuminuria predict better outcomes, there is no randomized evidence that targeting a lower albuminuria level improves clinical outcomes.

The risk stratification heat map is difficult to memorize: we offer the alternative suggestion that for people with CKD but without diabetes, eGFR be determined when there is an important change in health status and when considering prescribing a medication affected by eGFR, and that albuminuria be assessed initially and reassessed to assess the etiology of new edema and whenever knowledge of albuminuria will affect management, such as prescribing RAS blockade. After the first 2 eGFR values have established the diagnosis of CKD and provided initial information about trajectory, we suggest routinely reassessing eGFR at clinically relevant intervals, more often the lower the eGFR, the more rapid the decrease in eGFR, and the higher the albuminuria at baseline. This suggestion is provided as an addition to usual clinical care and monitoring and not as a substitute for clinical judgment.


**Definition of CKD Progression**

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 ($\geq 90$ [G1], 60–89 [G2], 45–59 [G3a], 30–44 [G3b], 15–29 [G4], <15 [G5]) $\text{mL/min/1.73 m}^2$. 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 $\text{mL/min/1.73 m}^2/\text{yr}$. A rapid drop means a decline in eGFR by a 25% or greater drop from baseline.
- 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**

We concur with recommendations 2.1.2 and 2.1.4. With respect to statement 2.1.3, we did not understand the rationale for including change between categories in the definition of progression given the arbitrary nature of category boundaries: we thought that a change, for example, in GFR from 80 to 60 $\text{mL/min/1.73 m}^2$ should have the same significance (in practice and research) as 75 to 56 $\text{mL/min/1.73 m}^2$, though one crosses a boundary and the other does not; however, we recognized the work validating the definition.\textsuperscript{49,50} We also note that by this definition, progression was not a significant predictor of ESRD when adjusted for most recent eGFR. Further work on the prognostic implications of changes in eGFR is needed. Rapid progression, defined as loss of eGFR $> 5 \text{ mL/min/1.73 m}^2$ per year, predicts vascular events, death, and ESRD,\textsuperscript{44 \text{[G3b]}, 15} which adds to our idea that it is a valid measure (ie, improves its construct validity). Additional GFR estimates increase the accuracy of the determination of rapid progression. The timing of routine interval re-evaluations for progression should be determined by the eGFR (the lower, the sooner), the rapidity of progression based on available values, and the clinical context. Health care practitioners should also remain sensitive to the possibility that a change in eGFR reflects an AKI that mandates prompt re-evaluation.

**Pediatric considerations.** The trend of GFR assessments over time is more relevant than a particular specific assessment. Children are in a unique position for expected growth and development inclusive of capacity for renal growth, maturation of renal function, and recovery from renal insult. In addition, children tend to have less nephrotoxic burden due to lower prevalence of chronic disease states compared with adults. Somatic growth of the child is the primary goal of pediatric care, which challenges renal growth and functional capacity to adapt to increased body demands. We endorse periodic GFR assessments (corrected for body surface area) correlated with somatic growth goals to evaluate progression and need for RRT.

**Other Factors That Predict Progression of CKD**

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**

In addition to the evidence-based risk factors listed in the guideline, a 2013 systematic review\textsuperscript{56} identified 2 risk-prediction models for patients with CKD that have acceptable measurement properties and are usable at the point of care for the prediction of ESRD.\textsuperscript{37,58} The first is a points-based pen and paper tool, which incorporates age, sex, eGFR, diabetes, hypertension, and hemoglobin to give a 5-year risk of ESRD. The C statistic was 0.89, generally regarded as excellent discrimination.\textsuperscript{57} This was derived in a primary care data set and has not been externally validated. The second, now known as the kidney function risk equation, is an externally validated online or smartphone calculator\textsuperscript{59} that uses age, sex, eGFR, urine ACR, albumin, phosphate, bicarbonate, and calcium to predict 2- and 5-year risk. These risk equations may be useful to further inform prognosis. However, whether use of these tools improves decisions about timing of specialist referral or interventions is not yet known.

**MANAGEMENT OF PROGRESSION AND COMPLICATIONS OF CKD**

**Individualizing Blood Pressure Targets and Treatments**

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)

**Commentary**

We concur with recommendations 3.1.1 through 3.1.3.

**Blood Pressure Target in Hypertensive Patients With CKD**

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)

**Commentary**

Though observational data consistently show that lower achieved blood pressures (BPs) are associated with better outcomes than higher BPs, the randomized evidence for further BP reduction to targets less than 140/90 mm Hg has significant limitations.

Data for patients without diabetes are derived from the long-term follow-up of the MDRD Study and AASK (African American Study of Kidney Disease) and from the REIN-2 (Ramipril Efficacy in Nephropathy 2) Study.60-62 None of the studies observed a clinically important statistically significant difference in cardiovascular outcomes. In terms of renal outcomes, a 2011 meta-analysis63 noted that there was inconsistent evidence of benefit with proteinuria; furthermore, the REIN-2 Study,61 conducted entirely in patients with proteinuria, did not show benefit. This last study has been criticized for not having achieved wide group separation in achieved BP. A 2013 meta-analysis64 (published since the appearance of the KDIGO guideline) observed a hazard ratio (HR) for ESRD of 0.79 (95% confidence interval [CI], 0.67-0.93) overall, 1.12 (95% CI, 0.67-1.87) in a highly heterogeneous analysis of patients without proteinuria, and 0.73 (95% CI, 0.62-0.86) in an analysis of patients with proteinuria (with low heterogeneity). We do not judge this finding robust because the absolute difference between groups in ESRD outcomes was just 9 events.

For people with diabetes and CKD, the evidence of kidney protection from a lower BP target derives from a single study of patients with A2 albuminuria and a mean age of 55 years65 and is confounded by the multiple cointerventions that were compared with usual care. However, in a broader group of patients with diabetes (but not CKD), ESRD was reported as an adverse outcome in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study (systolic BP < 120 vs 140 mm Hg) and was equivalent in both groups (relative risk [RR], 1.01; 95% CI, 0.84-1.21).66 Cardiovascular outcomes, summarized in a 2012 meta-analysis,67 were equivalent for mortality (RR, 0.76; 95% CI, 0.55-1.05) and myocardial infarction (RR, 0.93; 95% CI, 0.80-1.08), but risk for stroke was lower (RR, 0.65; 95% CI, 0.48-0.86), this last largely driven by the findings of the ACCORD Study.

In conclusion, we recommend that in patients without proteinuria who do not have diabetes, standard targets (140/90 mm Hg) should be used.

We assessed the evidence for a lower BP target in patients with proteinuria who do not have diabetes and for a lower BP target in patients with diabetes, regardless of proteinuria, as insufficient to recommend or suggest a lower target. We recognized the limitations in the evidence and the interpretations of other experts, including the CSN commentary on BP management,68 by concluding that either standard or lower target is reasonable in these patients.

**Implications Within Canadian Health Care**

Patients with CKD G1 to G3 and many with G4 are commonly managed in primary care in Canada. A uniform BP target reduces the need for repeat risk stratification and simplifies treatment goals and practice audit. **Not seeking a lower BP target will reduce by 0.5 to 1.0 the number of medications needed,**66 which is particularly relevant for those who pay for medications out of pocket. **Because targeting lower BP is resource intensive and associated with an increase in adverse events, we advise against its implementation in policy and quality initiatives.**

**Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers**

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

We concur with recommendations 3.1.6 to 3.1.7. We thought that recommendation 3.1.8 did not go far enough: ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial), which was a randomized trial conducted in people with and without CKD who were at high vascular risk, showed that the combination of full-dose angiotensin-converting enzyme (ACE) inhibitors and full-dose angiotensin receptor blockers (ARBs) increased the risk of hyperkalemia and AKI without reducing cardiovascular outcomes, renal outcomes, or death.69,70 Subgroup analysis showed no benefit in any CKD subgroup, though combined blockade lowered proteinuria more than single agents in this study, as in others. The VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) Study, conducted in people with diabetes, GFR of 30 to 90 mL/min/1.73 m², and urine ACR > 30 mg/mmol (published since the KDIGO guideline was written), also showed increased harm (AKI and hyperkalemia) from combination treatment.71 We recommend that the combination of ACE inhibitors and ARBs not be routinely used.

With respect to the recommendations concerning treatment of children (3.1.10-3.1.11), we agree with the recommendation of the intervention used in the ESCAPE (The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients) trial.72 target mean arterial pressure below the 50th percentile for age, based on the reduction (HR, 0.65; 95% CI, 0.44-0.94) in the outcome loss of 50% of GFR or ESRD in this randomized study of (mostly proteinuric) children with CKD.

Implications Within Canadian Health Care

We recommend not using ACE inhibitors with ARBs in primary care. Specialists should recognize that evidence that the combination alters clinically important outcomes is lacking, even in heavily proteinuric patients, and that adverse effects are increased.

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)

Commentary

See the CSN commentary on the KDIGO AKI guideline.73

Protein Intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (2Q) or without diabetes (2B) and GFR < 30 ml/min/1.73 m² (GFR categories G4-G5), with appropriate education.

Commentary

The beneficial effect of protein restriction, if any, is probably modest, and there are clinically important risks. Several well-designed randomized controlled trials have evaluated the efficacy of protein restriction in patients with progressive CKD. In patients with diabetes, a Cochrane review published in 200774 found that protein restriction to approximately 0.6 to 0.8 g/kg per day was associated with a nonsignificant reduction in the decline of GFR of 0.14 mL/min per month (95% CI, –0.06 to 0.34; P = 0.18; 7 studies).

In patients without diabetes, a 2009 Cochrane review showed a significant overall decrease in ESRD or death associated with a low-protein diet.75 However, studies that used moderate protein restriction (defined as 0.6 g/kg per day; 3 studies, 121 outcomes) showed no significant benefit, whereas studies that used a more stringent protein restriction of 0.3 to 0.6 g/kg per day showed benefit (RR for ESRD or death, 0.63; 95% CI, 0.48 to 0.83; P = 0.0009; 7 studies, 160 outcomes). It is possible that protein restriction to 0.3 to 0.6 g/kg per day reduces renal progression, but that less severe restriction does not.

Important long-term safety risks are associated with low- and very low-protein diets in patients with advanced CKD. Nutritional studies in patients with CKD suggest that protein intake can be safely lowered to 0.6 g/kg per day providing caloric goals are met, dietary protein is of high biological value, and metabolic acidosis is avoided.76-79 However, a very low-protein diet has been associated with increased mortality: in the long-term follow-up of the MDRD Study,80 assignment to a very low-protein diet (0.3 g/kg per day) was associated with an increased risk of death (HR, 1.92; 95% CI, 1.15-3.20).
A number of factors make the interpretation of study results on protein restriction difficult. Variability in CKD stages, degree of proteinuria, type of dietary protein provided, patient adherence to diet, physician enthusiasm, BP control, and glycemic control may have affected the outcomes of the various published studies. Many of the studies on dietary intervention were published before the widespread use of RAS blockade. Because the proposed mechanisms of action of RAS blockade and protein restriction are similar (both reduce single-nephron mechanisms of action of RAS blockade and protein intake), it is questionable whether any effect of protein restriction would be additive to the effect of RAS blockade. Because of the role of dietary proteins on both renal hemodynamics and the accumulation of metabolic toxins, evaluation of the true impact of protein restriction is complex. For instance, protein restriction may delay the initiation of dialysis therapy by reducing the production of uremic toxins, thereby reducing serum urea levels and clinical manifestations of uremia, which are both factors in the decision to start dialysis therapy, while having limited impact on CKD progression per se.

The available evidence does not support, and we do not recommend, routine protein restriction (<0.8 g/kg per day) in patients with CKD. Protein restriction may be reasonable for some patients if certain conditions are all met: a well-nourished patient who understands the risks and benefits and the uncertainty about them, who wishes and has the resources to comply with dietary prescription, and who has access to expert ongoing dietary supervision and nutritional assessment, preferably by a dietitian.

**Avoiding High Protein Intake**

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

**Pediatric considerations.** Protein restriction should not be undertaken in children with CKD because of limited data on efficacy and the concern that growth may be affected. In a meta-analysis published in 2007, no significant differences were found in number of renal deaths (RR, 1.12; 95% CI, 0.54-2.33), progression of kidney disease (mean difference in creatinine clearance at 2 years, 1.47; 95% CI, −1.19 to 4.14), or growth (mean difference in weight, −0.13; 95% CI, −1.10 to 0.84; mean difference in height, −1.99; 95% CI, −4.84 to 0.86). However, some concerns remained regarding adverse effect on growth as some anthropometry data suggested lower growth velocity with protein restriction.

**Glycemic Control and Hemoglobin A1c Targets**

3.1.15: We recommend a target hemoglobin A1c (HbA1c) 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 HbA1c target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (1B)

3.1.17: We suggest that target HbA1c 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**

Although evidence supporting intensive glycemic control in type 2 diabetes consistently demonstrates a reduced rate of microvascular complications, the time until benefit is long. In the ACCORD Study, a median treatment duration of 3.7 years was required to reduce incident microalbuminuria or macroalbuminuria. In other studies, the time until benefit was even longer, ranging from 5.5 to 14 years. Reduction in the progression of existing microalbuminuria was demonstrated in the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial, with a time until benefit of 2 years. In all these trials, control groups maintained at less stringent hemoglobin A1c (HbA1c) levels (7.3%-9.4%) had rates of diabetic complications that were similar to treatment groups for many years. As the burden of comorbidity and functional impairment increases, the expected survival benefit of intensive glycemic control diminishes because of competing risk. A decision analysis quantified the expected increase in survival from more stringent
HbA1c control: an increase of 106 days in quality-adjusted life-years in people aged 60 to 64 years who were in good health (these patients had a life expectancy of 14.6 years), an increase of 44 days in those with some comorbidity (life expectancy, 9.7 years), and an increase of just 8 days with more substantial comorbidity (life expectancy, 4.8 years). Finally, age has been shown to be an independent risk factor for hypoglycemia with intensive glycemic control. Synthesizing this evidence, we suggest a target HbA1c between 7.0% and 8.5%, depending on patient characteristics and values.

Sodium Intake

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.

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.

Commentary

We concur with recommendation 3.1.19.2. With respect to recommendations 3.1.19 and 3.1.19.1, although reducing sodium intake to the level recommended by the guideline (<90 mmol [equivalent to <2 g of sodium or <5 g of salt] with no lower bound), in both the general population and people with CKD, is known to reduce BP and measures of proteinuria, the evidence on the effects on progression of GFR or ESRD is limited. The best evidence comes from 2 observational studies that reported: (1) no difference in ESRD or cardiovascular outcomes across 3 tertiles of sodium intake in patients not on ARBs and (2) an increased risk of progression to ESRD in the highest third of sodium intake (mean sodium level, 5.3 g/d) compared with the middle third (mean level, 4.1 g/d), but no difference between the middle and lowest thirds. A systematic review (published since the KDIGO guideline) reported a consistent association between high sodium intake (>4.6 g/d) and adverse renal outcomes, but the association between low (<2.3 g/d) versus moderate (2.3-4.6 g/d) was inconsistent. Also published since the KDIGO guideline, a large observational study conducted in patients at high vascular risk showed no relationship between sodium intake and either progressive loss of GFR or progression of proteinuria. To date, no adequately powered long-term randomized clinical trial has evaluated the causal relationship between sodium intake and renal outcomes.

In terms of important nonrenal outcomes, studies of mostly nonrenal populations with and without hypertension were summarized in a meta-analysis of studies published in or before 2011, performed for the World Health Organization Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health. In trials reducing sodium intake compared with control or no intervention, systolic BP decreased by 3.4 (95% CI, 2.5-4.3) mm Hg, and diastolic BP, by 1.5 (95% CI, 0.98-2.1) mm Hg. Reductions of this magnitude would be expected to reduce heart disease and stroke; in the same review, higher sodium intake was associated with increased risk of stroke and fatal stroke (risk ratios of 1.24 [95% CI, 1.08-1.43] and 1.63 [95% CI, 1.27-2.10], respectively), inconclusive effects on cardiovascular disease or coronary heart disease (risk ratios of 1.12 [95% CI, 0.93-1.34] and 1.04 [95% CI, 0.86-1.24], respectively), and an increased risk of fatal coronary heart disease events (risk ratio, 1.32; 95% CI, 1.13-1.53). Recent prospective cohort studies reported a J-shaped association between sodium intake and cardiovascular disease. A study of a secondary prevention population (n = 28,880) reported the lowest cardiovascular disease risk at 4 to 6 g/d of sodium, intakes < 3 g (HR, 1.19; 95% CI, 1.02-1.39) and >7 g (HR, 1.53; 95% CI, 1.26-1.86) associated with increased risk of cardiovascular mortality, and no relationship with loss of GFR or ESRD or progression of proteinuria. A second study, of patients with type 1 diabetes (n = 2,807), reported a similar J-shaped association with all-cause mortality. Three other prospective cohort studies have reported inverse associations with increased risk of cardiovascular death with low intake of sodium.

In summary, evidence from the literature indicates reductions in sodium intake lead to lower BP in the general population and in people with hypertension, who are the subject of general recommendations; however, population recommendations are beyond the scope of the guideline. We recognize that practitioners may wish, for consistency, to give advice to patients with renal disease that is aligned with population health recommendations and standard preventative practice (Health Canada recommends 1.5 g/d as an adequate intake and 2.3 g/d as a tolerable upper limit; the Canadian Hypertension Education Program recommends “reducing towards” 2.0 g/d).

However, consideration of the direct evidence available in renal populations and populations with vascular disease led us to different conclusions about what we could consider an evidence-based
therapeutic diet for patients with CKD. In general, among people with renal disease, those who had the fewest outcomes were those with mean urinary sodium excretion corresponding to intakes of 2.7 to 3.3 g/d compared with higher intakes. Accepting that these observational data are low-quality evidence on which to base a recommendation for therapy, we suggest reducing sodium intake in patients whose estimated intake greatly exceeds these values. We do not support the recommendation of <2 g/d because of the absence of evidence for this threshold. Alternative interventions are available to reduce BP that have been shown to reduce clinically important outcomes, and there are the possibilities of harm from malnutrition and from the social, cultural, and financial difficulties associated with changes from a person’s normal diet. We recognize and respect the opinions of other committees, including the CSN commentary on BP management, which was independent of our committee.

With respect to resistant hypertension or edema, a recent randomized crossover trial in hypertensive patients with stage 3 to 4 CKD who were counseled by a dietitian to follow a low-sodium diet (<2.3 g/d) and then randomly assigned to receive either 120 mmol/d of sodium versus placebo (ie, <2.3 g/d vs 5 g/d) showed significant short-term changes in BP, kidney function, and fluid parameters, favoring the lower sodium diet over 2 weeks, but no long-term data are available. Optimal sodium restriction for those with resistant hypertension or edema is not known.

Implications Within Canadian Health Care

In the developed world, much of the population sodium consumption derives from processed food. In Canada, nearly 80% of sodium intake is attributable to the use of processed and restaurant foods, and average sodium intake of Canadians is estimated to be 3.4 g/d. Therefore, we believe the focus of dietary sodium reduction should be placed on reducing the consumption of processed and restaurant foods, which has the additional benefit of avoiding phosphate additives. We also recommend encouraging patients to choose lower-sodium alternatives at the point of food purchase rather than to discourage the use of salt in cooking. This likely would aid patients to choose a diet higher in fresh fruits and vegetables, which is also consistent with the observational data that diets rich in fruit and vegetables are associated with better renal outcomes (section 3.1.4). However, we recognized that some frail but independent elderly people may rely on processed food and that for them, other options may not be feasible. The focus for patients with poor intake of food and declining health should be to avoid dietary restrictions in the hope of encouraging better food intake and reducing the risk or progression of malnutrition.

Hyperuricemia and Lifestyle

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 asymptomatic or symptomatic hyperuricemia or asymptomatic hyperuricemia in order to delay progression of CKD. (Not Graded)

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)

Commentary

We concur with recommendation statements 3.1.20 and 3.1.21.

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)

Implications Within Canadian Health Care

Access to dietitian support is generally good in Canada, but current resources would not permit long-term supervision, or even assessment, of all people with CKD. However, in remote areas, there are Canadians who would not have easy access to supervision by a dietitian. Not adopting protein restriction routinely in patients with CKD avoids the unintended but inevitable consequence of redirection of this limited resource away from those (with and without CKD) who receive specific referral on the basis of ability to benefit.

A more liberal suggestion about sodium intake and protein intake may enhance quality of life and adherence, as well as reducing the proportion of patients who would be advised to make changes. Patients with GFRs > 30 mL/min/1.73 m² rarely experience hyperphosphatemia, acidosis, or hyperkalemia. Though hyperparathyroidism occurs in 25% to 60% of patients with GFRs of 30 to 60 mL/min/1.73 m², there is no direct evidence that managing hyperparathyroidism through diet in patients with GFR > 30 mL/min/1.73 m² prevents clinically important outcomes. Our focus in detection and dietary management of these problems can appropriately remain on the fewer patients with GFRs < 30 mL/min/1.73 m².

We recognize the financial costs to patients for special diets, particularly to those living in northern communities. We also recognize the cultural and societal importance of food to our...
First Nations’ people and all Canadians, and we acknowledge the potential negative outcome of over-restrictive therapeutic dietary regimens. We suggest that clinicians take into account culturally appropriate and individualized approaches to nutritional interventions, whenever possible, when they advise their patients on dietary habits. This will likely enhance compliance and limit potential adverse outcomes as a result of evoking fear of food in patients and over-restricting their intake.

Anemia

**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 m² (GFR categories G1-G2);
- at least annually in people with GFR 30–59 ml/min/1.73 m² (GFR categories G3a-G3b);
- at least twice per year in people with GFR < 30 ml/min/1.73 m² (GFR categories G4-G5).

**Commentary**

We concur with recommendations 3.2.1 and 3.2.2, but note that these are thresholds for the identification of the problem, not for treatment. Recommendation 3.2.3 concerns screening for anemia in patients with CKD. As >50% of patients with eGFRs < 30 mL/min/1.73 m² have anemia, we suggest screening for anemia in these patients, and if identified, further clinical evaluation of the contributing causes for these patients, but the optimal frequency of rescreening will depend on the patient’s comorbidities, GFR, and hemoglobin. There is insufficient evidence to provide suggestions or recommendations on the minimum frequency of hemoglobin remeasurement, beyond the application of clinical judgment, and no evidence to support annual screening in people with GFRs of 30 to 59 mL/min/1.73 m². Management of anemia is discussed in the CSN commentary on the KDIGO anemia guideline.

**Metabolic Bone Disease**

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 m² (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 m² (GFR categories G3b-G5), as information may be misleading or unhelpful. (2B)

**Commentary**

We concur with recommendation 3.3.2. With respect to recommendation 3.3.1, in 2 large cohorts (NHANES [National Health and Nutrition Examination Survey] and KEEP [Kidney Early Evaluation Program]) of participants with eGFRs < 45 mL/min/1.73 m², calcium values were in the normal range in 89% and 92%, respectively, and phosphorus values were in the normal range in 87% and 90%, respectively. While abnormal parathyroid hormone (PTH) values were more prevalent (36% and 31% within normal range), it is unlikely that their recognition is important as treatment for abnormal PTH values have not been demonstrated to affect clinically important outcomes, even in those with advanced CKD or ESRD. There is insufficient evidence to provide any general suggestion on the need to screen for metabolic bone disease in patients with CKD and GFRs > 30 mL/min/1.73 m².

Laboratory abnormalities reflecting metabolic bone disease are more prevalent in patients with GFRs < 30 mL/min/1.75 m². We suggest screening these patients, and rescreening depending on comorbidity, GFR, and the values observed on the first occasion, though we recognize that evidence-based strategies for the management of these abnormalities are not available.

**Target Serum Phosphate Levels**

3.3.3: In people with GFR <45 ml/min/1.73 m² (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (2C)

**Commentary**

There is insufficient evidence to recommend the measurement or clinical targets for serum phosphate in people with GFRs < 45 mL/min/1.75 m². Elevated serum phosphate is associated with increased mortality and vascular and valvular calcification; however, achievement of clinical targets for these parameters over time has not been associated with improved survival in ESRD populations. With the exception of advice to avoid processed food because of the prevalence of phosphate additives, restricting to low-phosphate foods is difficult without incurring protein restriction, which may lead to

Am J Kidney Dis. 2015;65(2):177-205
malnutrition and adverse outcomes (see recommendation 3.1.3).

Calcium-based phosphate binders are widely used and inexpensive compared with non–calcium-based phosphate binders, but a 2013 meta-analysis of 4,622 patients in 11 randomized controlled trials suggested an increase in mortality from their use, compared with non–calcium-based binders.118 This meta-analysis is limited by evidence of publication bias118,119: Duval’s trim and fill analysis, which adjusts for publication bias, resulted in loss of loss of statistical significance for the adjusted intervention effect (0.82; 95% CI, 0.64-1.04).119 Exclusion of small studies (<50 events) resolves heterogeneity, attenuates the effect size, and results in loss of statistical significance (RR, 0.93; 95% CI, 0.82-1.04).119 Furthermore, interpretation of the study is also problematic because of a lack of placebo controls: were we to give credit to the results, we do not know whether they mean that calcium-containing binders are harmful (compared to no intervention) or that sevelamer, the most extensively studied noncalcium binder, is beneficial (compared to no intervention). Because of these uncertainties, we are unable to make a recommendation or a suggestion in this area: either using or not using phosphate binders and either using a calcium-containing or non–calcium-containing binder are reasonable.

**Optimal PTH Level**

3.3.4: In people with GFR <45 ml/min/1.73 m² (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)

**Commentary**

There is insufficient evidence to suggest the measurement or clinical targets for hyperphosphatemia, hypocalcemia, and high PTH in people with GFRs < 45 mL/min (see previous comments on recommendation 3.3.3). The course of action outlined or a less active approach are both reasonable.

**Nutritional Vitamin D and Calcitriol**

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)

**Commentary**

We agree that there is no randomized evidence of clinically important benefit from suppression of PTH in patients with CKD, either by nutritional or activated (hydroxylated) vitamin D.

The guideline is silent on the appropriate use of both nutritional vitamin D and hydroxylated vitamin D as nutritional supplements in patients with CKD. Vitamin D (cholecalciferol) is an essential nutritional compound, and its deficiency in the diet leads to nutritional-related deficiency diseases such as rickets and osteomalacia.120 Many populations in the developed world have a high prevalence of vitamin D deficiency (eg, 32% of Canadians).121 Because the prevalence of deficiency and insufficiency are higher in people with CKD than in the general population122 and lower levels are associated with mortality in people with CKD,123 routine supplementation at a higher dose than the general population recommendation has been suggested (4,000 rather than 1,000 IU/d).124 A meta-analysis of observational and randomized studies of nutritional vitamin D in therapeutic doses (~10,000 IU/d) showed increases in serum vitamin D levels in all CKD stages, reduction in PTH, and minimal effect on serum calcium and/or phosphate levels.125

Activated vitamin D (1,25-dihydroxyvitamin D; calcitriol) is a hormone with specific endocrine functions, including PTH suppression, and needs to be clearly distinguished from its precursor, the nutritional compound cholecalciferol. Circulating calcitriol derives at least in part from renal 1α-hydroxylation from the precursor, but it is also hydroxylated locally in other tissues, where it produces autocrine and paracrine effects.126 These effects have been implicated in immune function, prevention of malignancy, and reduced cardiovascular disease occurrence in people with and without CKD.123,124,126

Because of reduced renal hydroxylation, calcitriol deficiency is prevalent in patients with CKD and is thought to contribute to hyperparathyroidism, metabolic bone disease, and perhaps vascular calcification, though serum levels do not correlate with markers of metabolic bone disease.124 A meta-analysis of vitamin D analogues, such as calcitriol, used pharmacologically showed uncertain reductions in PTH and increases in calcium and phosphate levels. Clinically important renal outcomes could not be assessed.

Because randomized studies of clinically important outcomes are lacking, we were not able to recommend the use of nutritional vitamin D, alfacalcidol, or calcitriol in patients with CKD. Derangements of the bone and calcification systems are less prevalent and severe in patients with GFRs > 30 ml/min/1.73 m², and we suggest following general population recommendations for supplementation of nutritional vitamin D (range of 800–1,000 IU daily).128,129 without routine measurement of PTH or vitamin D levels. In patients with GFRs < 30 ml/min/1.73 m², either supplementing, or not supplementing, at doses up to ~4,000 IU daily are both reasonable, based on
clinical judgment and the patient’s preferences. The use of alfacalcidol or calcitriol as a nutritional supplement in patients with CKD is supported even less by evidence of benefit, though there is strong evidence of deficiency, especially in those with the lowest levels of GFR. We consider either using or not using these analogues to be reasonable.

**Bisphosphonates in People With CKD**

3.3.6: We suggest not to prescribe bisphosphonate treatment in people with GFR <30 ml/min/1.73 m² (GFR categories G4-G5) without a strong clinical rationale. (2B)

**Commentary**

We concur with this recommendation; because this is a prophylactic measure that has no evidence for benefit in people at this range of GFR, it was difficult to understand what might ever constitute a strong clinical rationale for using it.

**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**

Lower serum bicarbonate is associated with more rapid progression, and one small randomized controlled trial suggests that treating patients with eGFRs < 30 mL/min/1.73 m² and serum bicarbonate concentrations < 20 mmol/L may decrease progression of CKD. This finding needs to be confirmed in other clinical trials, but the intervention is safe in most clinical contexts. Either prescribing or not prescribing bicarbonate is reasonable. Bicarbonate is unpalatable to some patients and in tablet form incurs expense. Substitution of baking soda from a food store (1/4 teaspoon = 1 g of sodium bicarbonate) may be helpful.

**OTHER COMPLICATIONS OF CKD**

**Patients With CKD and Cardiovascular Disease**

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**

We concur with recommendation 4.1.1. With respect to the recommendation 4.1.2 regarding patients with ischemic heart disease, we agree that there are observational data to support improved health outcomes in people with CKD by offering them the same standard of care for ischemic heart disease as in the general population. However, there are some considerations in people with CKD that may appropriately alter their care. For example, in patients with low GFRs at high risk of contrast-induced nephropathy and stable ischemic heart disease, clinical judgment is required in terms of timing of angiography and revascularization. In patients with CKD who have made an advance decision not to receive kidney replacement therapies to manage kidney failure, more conservative approaches to managing ischemic heart disease may be chosen.

Regarding recommendation 4.1.3 concerning antiplatelet medications, patients with low GFRs are generally at increased bleeding risk, and antiplatelet medications increase the risk of major bleeding by 33%. There is uncertain benefit of antiplatelet agents in people with GFRs < 15 mL/min/1.73 m². Either prescribing or not prescribing antiplatelet medication to patients with stable vascular disease and CKD is reasonable.

We concur with recommendations 4.1.4 to 4.1.5.

**N-Terminal Pro-Brain Natriuretic Peptide and Troponin**

4.2.1: In people with GFR <60 ml/min/1.73 m² (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)

4.2.2: In people with GFR <60 ml/min/1.73 m² (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (1B)

**Commentary**

We concur with recommendation 4.2.1. With respect to recommendation 4.2.2, though the diagnostic test accuracy of the elevated troponin for acute coronary syndrome in patients with CKD is not optimal, it has a very good prognostic accuracy. Elevated troponin in patients with CKD is actually more predictive than in patients without CKD of myocardial infarction and death within 30 days (adjusted ORs of 2.5 [95% CI, 1.8-3.3] and 1.7 [95% CI, 1.3-2.2], respectively).
Noninvasive Cardiac 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

Most of the literature about evaluation for coronary artery disease in patients with CKD comes from the evaluation of kidney transplant candidates. In these studies, a majority of patients already have ESRD or an advanced stage of CKD. Reports of diagnostic test accuracy (sensitivity and specificity) of noninvasive cardiac testing in patients with CKD are highly variable (inconsistent); however, all the widely used noninvasive tests are generally less accurate (typically less sensitive and less specific) in patients with advanced CKD than in those without. Table 1 summarizes the test accuracy for available noninvasive cardiac testing in patients with CKD based on our data extraction from papers identified in a 2011 systematic review.

Peripheral Artery 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)

Commentary

We do not concur that all adults with CKD should be regularly examined for peripheral artery disease. We are not aware of any studies showing health benefit from periodic examination in this area. We also noted that the diagnostic test accuracy of commonly used studies like ankle-brachial index is questionable in CKD populations because of the increased prevalence of vessel calcification.

Table 1. Summary of Accuracy of Noninvasive Testing in Pretransplantation CKD Patients

<table>
<thead>
<tr>
<th>Noninvasive Cardiac Testing</th>
<th>No. of Studies</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>11</td>
<td>0.44 (0.27-0.62) to 0.96 (0.78-1.00)</td>
<td>0.60 (0.36-0.81) to 1.00 (0.81-1.00)</td>
</tr>
<tr>
<td>Myocardial perfusion scintigraphy</td>
<td>7</td>
<td>0.29 (0.08-0.58) to 0.92 (0.62-1.00)</td>
<td>0.50 (0.16-0.84) to 0.88 (0.69-0.97)</td>
</tr>
<tr>
<td>Exercise stress electrocardiography</td>
<td>2</td>
<td>0.36 (0.21-0.54) to 1.00 (0.29-1.00)</td>
<td>0.00 (0.00-0.97) to 0.91 (0.83-0.96)</td>
</tr>
<tr>
<td>Exercise ventriculography</td>
<td>1</td>
<td>0.50 (0.23-0.77)</td>
<td>0.67 (0.43-0.85)</td>
</tr>
<tr>
<td>Digital subtraction fluorography</td>
<td>1</td>
<td>0.78 (0.61-0.90)</td>
<td>0.66 (0.51-0.79)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CKD, chronic kidney disease.

Regular Podiatric Assessment

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

Commentary

We do not concur that all adults with CKD should be regularly examined for peripheral artery disease.

Adjusting Drug Doses for Renal Clearance

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)

Commentary

We concur with recommendation 4.4.2. With respect to recommendation 4.4.1, there are limitations to the different estimating GFR equations when used for drug dosing. Some pharmacokinetic studies have excluded patients with decreased kidney function, making it difficult to assess drug dosing in these patients. Furthermore, when pharmacokinetic studies have been performed, kidney function was, in the past, usually estimated using the Cockcroft-Gault equation. Although the MDRD Study and CKD-EPI equations have been validated in large populations for assessing renal function, all estimating equations for GFR have their limitations, perhaps the greatest being their residual inaccuracy (eg, for CKD-EPI, 13% of estimates differ from measured GFR by >30%). However, measuring GFR directly, though more accurate, is rarely practical and is costly, so we focus on how best to use the equations.
It is important to recognize that both the MDRD Study and CKD-EPI equations estimate GFR normalized to body surface area, which is useful in assessing the presence of kidney disease and summarizing across populations, whereas what is needed for drug dosing is an estimate of absolute clearance (ie, in milliliters per minute, not milliliters per minute per 1.73 m²). Using CKD-EPI–estimated GFR to guide drug dosing may lead to underdosing larger people and overdosing smaller people or people with amputations. We recommend back calculation to an absolute clearance (using an anthropometric estimate of the patient’s body surface area) in people who are clearly larger or smaller than the average 1.73-m² person. When absolute clearances calculated from MDRD Study equation estimates were compared with measured GFR, with Cockcroft-Gault and with ideal-body-weight Cockcroft-Gault, concordance (percentage agreement on the stratum of kidney function) was 75% to 78%. Monitoring of patients’ responses to treatment, renal function in the case of nephrotoxic drugs, and drug levels when applicable is essential.

Sick-Day Rules: Advice to Stop Certain Medications When Risk for AKI is High

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m² (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)

Commentary

We concur with recommendation 4.4.3. Though direct evidence of benefit of this strategy is lacking, it is highly likely that continuing these agents under these circumstances would lead to harm, and possible that some patients will be able to learn sick-day rules and benefit from them.

Nonprescription Medications and Herbal Products

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)

Commentary

We concur with recommendation 4.4.4. Patients should always check with pharmacists when purchasing over-the-counter products as many products contain ingredients that can accumulate (eg, magnesium supplements and phosphate-containing laxatives) or cause nephrotoxicity (especially nonsteroidal anti-inflammatory drugs) in patients with CKD. With respect to recommendation 4.4.5, although herbal products are commonly used, their pharmacokinetics and pharmacodynamics in patients with CKD have not been well studied. However, there are many case reports with various herbal products causing nephrotoxicity and therefore these agents should be avoided in all patients.144

Implications Within Canadian Health Care

Canada is a multicultural society and we recognize that many patients may have cultural and spiritual practices that involve herbs about which little is known in our Western medical model. We recommend respectful negotiation with patients and families over these issues.

Metformin, Lithium, and Calcineurin Inhibitors

4.4.6: We recommend that metformin be continued in people with GFR ≥45 ml/min/1.73 m² (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m² (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m² (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)

Commentary

We concur with recommendation 4.4.7. With respect to recommendation 4.4.6, metformin is renally excreted and its clearance is proportional to GFR. We suggest dose reduction in proportion to the GFR.145-148

Based on indirect evidence, we suggest that patients be advised not to take metformin on days when they may experience AKI: for example, around surgery, angiography, and if they are unwell at home (sick-day rules; in keeping with 4.4.3).

GFR of 30 to 60 mL/min/1.73 m². We agree that metformin may be used in patients with GFRs as low as 30 mL/min/1.73 m². In a Cochrane meta-analysis of 347 studies, there was no case of lactic acidosis in either 70,490 metformin patient-years or 55,451 non-metformin patient-years.149 This review concluded that there is no evidence from trials or cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other antihyperglycemic agents. In patients with creatinine clearances < 40 mL/min, plasma concentrations of lactate did not correlate with metformin concentrations or metformin dose.150 In 1,572 patients with GFRs of 30 to 60 mL/min/1.73 m², metformin use, compared with other glucose-lowering therapies, was associated with a reduction in 2-year mortality;
People With CKD and Cancer

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

In addition, low GFR may represent an important comorbidity and risk factor for adverse outcomes that should be considered in the overall treatment plan.

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 m² (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the KDIGO Clinical Practice Guideline for AKI including:

- Avoidance of high osmolar agents (1B);
- Use of lowest possible radiocontrast 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 m² (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 m² (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 < 30 ml/min/1.73 m². Patients should have relatively stable renal function, be at low risk for AKI, and be likely to comply with sick-day rules; obese patients may benefit most. Because the direct evidence is limited, this is not a recommendation or a suggestion.

When resources permit, renally adjusted doses of sitagliptin may be a useful and safe alternative, which like metformin is not associated with weight gain. However, in patients who are beyond monotherapy, metformin may be combined with sitagliptin for additive hypoglycemic effects. Two studies of sitagliptin in a total of 517 patients with diabetes and CKD have been conducted and reported outcomes similar to those observed in studies in unselected patients with diabetes, but recommendations about safety in CKD are based on pharmacokinetics more than on extensive experience.

Commentary

We agree with these recommendations on the use of imaging studies. In terms of the recommendation regarding radiocontrast, we advise referring to the CSN commentary on the KDIGO AKI guideline.

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 m² (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 m² (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)

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)

Commentary

We concur with recommendations 4.6.1 to 4.6.7.1 (though see comments concerning the implications for Canadian health care for 4.6.1 and 4.6.4). With respect to CKD and the risk of AKI, we advise reviewing the CSN commentary on the KDIGO AKI guideline.73

Implications Within Canadian Health Care

With respect to recommendation 4.6.1, influenza vaccine is free in Canada for high-risk populations (individuals with renal disease and diabetes mellitus, infants, older adults, etc). Pneumococcal vaccine is publicly funded for patients with CKD in all provinces except Saskatchewan, where it is publicly funded for transplant recipients.160 In Canada, these vaccines would normally be given by the primary care provider, which facilitates tracking and revaccination.

With respect to recommendation 4.6.4, fiscal responsibility and cost-benefit versus risk analysis would place emphasis on immunizing those with CKD most likely to choose and require future dialysis or renal transplantation.161

CKD Management Programs

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)

Referral to Nephrologists

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 m² (GFR categories G4-G5).
Commentary

To date there has been no randomized controlled trial to assess which patients would benefit from nephrology referral and such a trial would be hard to conduct. Referral recommendations in the literature are inconsistent. Moreover, referral also depends upon the comfort of the patient’s primary care provider in managing CKD. We agree with a threshold of GFR < 30 mL/min/1.73 m² for referral to a nephrologist, though we recognized that it is reasonable not to refer some patients whose GFR is below this threshold if the GFR is stable and the diagnosis is relatively clear, or if very advanced age or the presence of comorbidity indicates a short life expectancy. We disagreed with the KDIGO recommendations for nephrology referral in the domain of AKI and the level of proteinuria for which patients may need referral. AKI in the primary care setting can often be effectively managed there with treatment of the precipitating cause (such as intercurrent illnesses and volume contraction), temporary discontinuation of RAS blockade and nonsteroidal anti-inflammatory medications, and correction of obstruction. A nephrologist or internist with an expertise in kidney disease should be sought in patients with an abrupt sustained decrease in eGFR > 20% (opinion-based threshold) after excluding reversible causes, or if there are features suggestive of a diagnosis other than prerenal azotemia or acute tubular necrosis.

It should be recognized that the vast majority of patients with stage 3 CKD do not progress to ESRD but die mainly from cardiovascular causes. Primary care intervention for cardiovascular risk reduction should be strongly considered.

Regarding proteinuria, KDIGO recommends referral to nephrology when ACR is ≥30 mg/mmol or PCR is ≥50 mg/mmol as these patients are at risk for cardiovascular mortality and morbidity and RRT. Although there are few data on the specific threshold for proteinuria that will identify those who benefit from nephrology referral, the higher the proteinuria, the greater the risk of ESRD. Immunosuppressive medications are generally not indicated unless proteinuria is > 1 g/d (ACR ≥ 60 mg/mmol or PCR ≥ 100 mg/mmol) and kidney biopsy in North America is generally not undertaken when kidney function is stable and proteinuria is < 1 g/d. These patients are treated with nonspecific therapy that can be instituted by primary care. We recommend referral to nephrology if there is persistent proteinuria with protein excretion > 1 g/d (ACR ≥ 60 mg/mmol or PCR ≥ 100 mg/mmol) as at this level of proteinuria, renal biopsy may be indicated and immunosuppressive medications may need to be considered. In addition, we thought that a nephrologist’s opinion may be beneficial if patients do not tolerate renal protective medications. Other reasons for referral, in addition to those listed in the guideline, are uncertainty about the diagnosis, suspected polycystic kidney disease or hereditary nephritis, inability to meet BP goals, severe electrolyte abnormalities, recurrent nephrolithiasis, unexplained or unexpected low GFR, or change in GFR, especially in the nonelderly.

Referral for Planning for RRT

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)

5.2.1: We suggest that people with progressive CKD should be managed in a multidisciplinary care setting. (2B)
are at high risk of ESRD and have eGFRs < 30 mL/min/1.73 m², those with rapid progression, or those with complex comorbidity may benefit from a multidisciplinary approach. Evidence supporting this recommendation is observational with potential for bias.

Characteristics of the Multidisciplinary Team

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)

Implications Within Canadian Health Care

As with recommendations 5.1.2 and 5.2.1, we recognized that the increased resources needed for the approach recommended in statement 5.2.2 might not be available in all programs and that policy makers have also to consider the opportunity costs. Some patients in rural areas will not have local access to all the recommended disciplines listed in these KDIGO recommendations. Imaginative and flexible models of care are needed to make best use of local resources and to support travel to tertiary centers when needed.

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 m². (2B)

5.3.2: Living donor preemptive renal transplantation in adults should be considered when the GFR is <20 mL/min/1.73 m², and there is evidence of progressive and irreversible CKD over the preceding 6-12 months. (Not Graded)

Commentary

See the CSN guideline on timing of the initiation of RRT. 171

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)

Commentary

Our CSN commentary committee concurred with the recommendations, but acknowledged the many barriers to this becoming reality, including limited resources, lack of funding, and lack of a coordinated approach to providing conservative renal therapy and palliative care to this patient group, as well as the possibility that general palliative support services may be available and have all the necessary expertise. As well, we acknowledge that some providers may be unwilling or unable to address issues required for patients to experience optimal end-of-life care, without RRT.

All CKD Programs and Providers to Delivery of Advanced Care Planning

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)

Commentary

In addition, we recommend that all efforts should be made to involve primary care providers in advance planning and end-of-life care.

Coordinated End-of-Life Care

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

We agreed with this recommendation in principle, though protocols are not always necessary to provide effective individualized care. However, we recognize that there is observational evidence 172 supporting a comprehensive conservative renal management program.

ACKNOWLEDGEMENTS

Guideline recommendations included in this article originally were published in Kidney International Supplement and were reproduced with permission from KDIGO.

Support: No financial support was required for the development of this commentary.

Financial Disclosure: Dr Akbari reports research funding from Ortho Biotech Inc, GE, Merck Frosst, Sanofi-Aventis, Boehringer Ingelheim, Pfizer, Amgen, and Bristol Myers Squibb. Dr Clase reports grants or honoraria from Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer-Ingelheim, and Baxter. Dr Battistella reports grants or honoraria from Amgen, Shire, and Takeda. Dr Feltmate reports honoraria from Pfizer and Janssen-Ortho. Dr Komenda reports grants or honoraria from Amgen, Astellas, Astellas, AstraZeneca, and Baxter. Dr Clase reports grants or honoraria from Amgen, Shire, and Takeda. Dr Fellman reports honoraria from Amgen, Shire, and Takeda. Dr Manns reports grants from Baxter and Abbot. The other authors declare that they have no relevant financial interests.
SUPPLEMENTARY MATERIAL

Item S1: Examples of level-of-evidence gradings that the commentary committee found difficult to understand. 

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.10.013) is available at www.ajkd.org

REFERENCES

34. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI)
and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis. 2010;56:486-495.


