KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD

Sankar D. Navaneethan, Nisha Bansal, Kerri L. Cavanaugh, Alexander Chang, Susan Crowley, Cynthia Delgado, Michelle M. Estrella, Cybele Ghossein, T. Alp Ikizler, Holly Koncicki, Wendy St. Peter, Katherine R. Tuttle, and Jeffrey William

The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the 2024 KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the management of chronic kidney disease (CKD). The KDOQI Work Group reviewed the KDIGO guideline statements and practice points and provided perspective for implementation within the context of clinical practice in the United States. In general, the KDOQI Work Group concurs with several recommendations and practice points proposed by the KDIGO guidelines regarding CKD evaluation, risk assessment, and management options (both lifestyle and medications) for slowing CKD progression, addressing CKD-related complications, and improving cardiovascular outcomes. The KDOQI Work Group acknowledges the growing evidence base to support the use of several novel agents such as sodium/glucose cotransporter 2 inhibitors for several CKD etiologies, and glucagon-like peptide 1 receptor agonists and nonsteroidal mineralocorticoid receptor antagonists for type 2 CKD in setting of diabetes. Further, KDIGO guidelines emphasize the importance of team-based care which was also recognized by the work group as a key factor to address the growing CKD burden. In this commentary, the Work Group has also assessed and discussed various barriers and potential opportunities for implementing the recommendations put forth in the 2024 KDIGO guidelines while the scientific community continues to focus on enhancing early identification of CKD and discovering newer therapies for managing kidney disease.

Complete author and article information provided before references.

Correspondence to S.D. Navaneethan (sankar.navaneethan@bcm.edu) or J. William (jhwillia@bidmc.harvard.edu)

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Because they are designed to reflect the views and recommendations of the responsible KDOQI Commentary work group and they are reviewed and approved by KDOQI and NKF leadership, KDOQI Commentaries are not peer reviewed by AJKD. This article was prepared by a KDOQI Commentary work group comprised of the authors. It was reviewed and approved by the NKF Scientific Advisory Board and the KDOQI.

Introduction

Chronic kidney disease (CKD) is estimated to affect 37 million people in the United States alone.[1] Hypertension and diabetes mellitus remain the most common risk factors for the development of CKD which increases the risk for cardiovascular morbidity and mortality.[2] Due to its largely asymptomatic nature and low rates of albuminuria testing, a vast majority of individuals with CKD are not aware of their condition, even in its later stages. The KDIGO 2024 CKD guidelines, last updated in 2012, offer a blueprint for providers to address these challenges in the following areas of CKD: identification/evaluation, risk assessment, management of progression and systemic complications, medication management, and team-based/collaborative care models.

Significant advances in CKD evaluation and management have advanced CKD care since the last KDIGO CKD guidelines were published in 2012. Multiple high-quality clinical trials of pharmacologic interventions show that several classes of medications reduce the risk of kidney failure, kidney function decline, death due to kidney disease, and cardiovascular disease (CVD) in adults with CKD and type 2 diabetes mellitus.[3-10] These drug classes, currently under further investigation in persons with nondiabetic CKD, include a nonsteroidal mineralocorticoid antagonist and glucagon-like peptide 1 (GLP1) receptor agonists. While these promising developments represent a renaissance in CKD care, ongoing studies and guideline development will be essential in helping practitioners understand how and when to utilize these medications in individuals with CKD.

In addition to pharmacologic advances in CKD, this last decade has also brought with it a more nuanced approach to the CKD population as a whole. This latest iteration of the guidelines incorporates guidance for children/adolescents and the elderly, as well as for sex and gender differences. The additional attention paid to these populations recognizes the complexity and nuance that each individual with CKD brings, from both medical and sociocultural perspectives. The efforts of the National Kidney Foundation (NKF) and American Society of Nephrology Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases have

resulted in widespread use of the updated, race-free estimated glomerular filtration rate (eGFR) CKD-EPI equations, no longer including a "race correction" for Black individuals to eliminate a contributing factor to structural racism in health care.[11] With renewed focus on providing a more complete picture of impaired kidney function, the new guidelines and commentary address the increasing use of cystatin C and the importance of the urinary albumin-creatinine ratio (UACR) in CKD screening, diagnosis, and management. Continued development and application of tools for estimating kidney function will increase patient and provider awareness of CKD, enabling effective CKD testing in high-risk populations, and provide optimized care to previously undiagnosed individuals. Once CKD is identified, multidisciplinary teams of providers are key in delivering high-quality care. The guidelines and commentary also address "team-based care," such as comprehensive medication management spearheaded by clinical pharmacists as well as effective pediatric-to-adult transitions of care, as just a few examples of the ways in which we are working to improve care delivery.

The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a Work Group to review the new 2024 KDIGO CKD guidelines. This commentary is the product of the KDOQI Work Group and presents the recommendations and practice points from the KDIGO guideline. Each recommendation is followed by a commentary and brief notes on clinical utility, implementation, and challenges.

Review and Approval Process for this Commentary

The KDOQI Steering Committee selected co-chairs and members of the KDOQI Work Group based on their clinical and research expertise as well as interest in the guideline process or familiarity with CKD quality metrics. During the selection process, particular emphasis was placed on identifying individuals with diverse perspectives and with experience in taking care of adult and pediatric patients with CKD.

KDOQI Work Group members worked in groups of 2 to review recent literature and provide commentary on the recommendations in the KDIGO guideline. The Work Group discussed the guideline via teleconference, and all Work Group members and KDOQI leadership reviewed and approved the commentary. Our review and commentary follow the same order and numbering scheme used in the KDIGO guideline. We did not provide commentary for every KDIGO recommendation and practice point. For those guideline recommendations that may have implications for US clinical care, we present comments and discuss its clinical utility and implementation in the United States. All material is reproduced with permission of KDIGO.

Evaluation of CKD

Detection and Evaluation of CKD

1.1.1. Detection of CKD

Practice Point 1.1.1.1: Test people at risk for and with chronic kidney disease (CKD) using both urine albumin measurement and assessment of glomerular filtration rate (GFR).

Practice Point 1.1.1.2: Following incidental detection of elevated urinary albumin-to-creatinine ratio (ACR), hematuria, or low estimated GFR (eGFR), repeat tests to confirm presence of CKD.

1.1.2. Methods for staging of CKD

Recommendation 1.1.2.1: In adults at risk for CKD, we recommend using creatinine-based estimated glomerular filtration rate (eGFRcr). If cystatin C is available, the GFR stage should be estimated from the combination of creatinine and cystatin C (creatinine and cystatin C-based estimated glomerular filtration rate [eGFRcr-cys]) *(1B)*.

1.1.3. Evaluation of chronicity

Practice Point 1.1.3.1: Proof of chronicity (duration of a minimum of 3 months) can be established by:

i. review of past measurements/estimations of GFR;
ii. review of past measurements of albuminuria or proteinuria and urine microscopic examinations;
iii. imaging findings such as reduced kidney size and reduction in cortical thickness;
iv. kidney pathological findings such as fibrosis and atrophy;
v. medical history, especially conditions known to cause or contribute to CKD;
vi. repeat measurements within and beyond the 3-month point.

Practice Point 1.1.3.2: Do not assume chronicity based upon a single abnormal level for eGFR and ACR, as the finding could be the result of a recent acute kidney injury (AKI) event or acute kidney disease (AKD).

Practice Point 1.1.3.3: Consider initiation of treatments for CKD at first presentation of decreased GFR or elevated ACR if CKD is deemed likely due to presence of other clinical indicators.

1.1.4. Evaluation of cause

Practice Point 1.1.4.1: Establish the cause of CKD using clinical context, personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and genetic and pathologic diagnosis (Figure 1).

Practice Point 1.1.4.2: Use tests to establish a cause based on resources available.

Recommendation 1.1.4.1: We suggest performing a kidney biopsy as an acceptable, safe, diagnostic test to evaluate cause and guide treatment decisions when clinically appropriate *(2D)*.

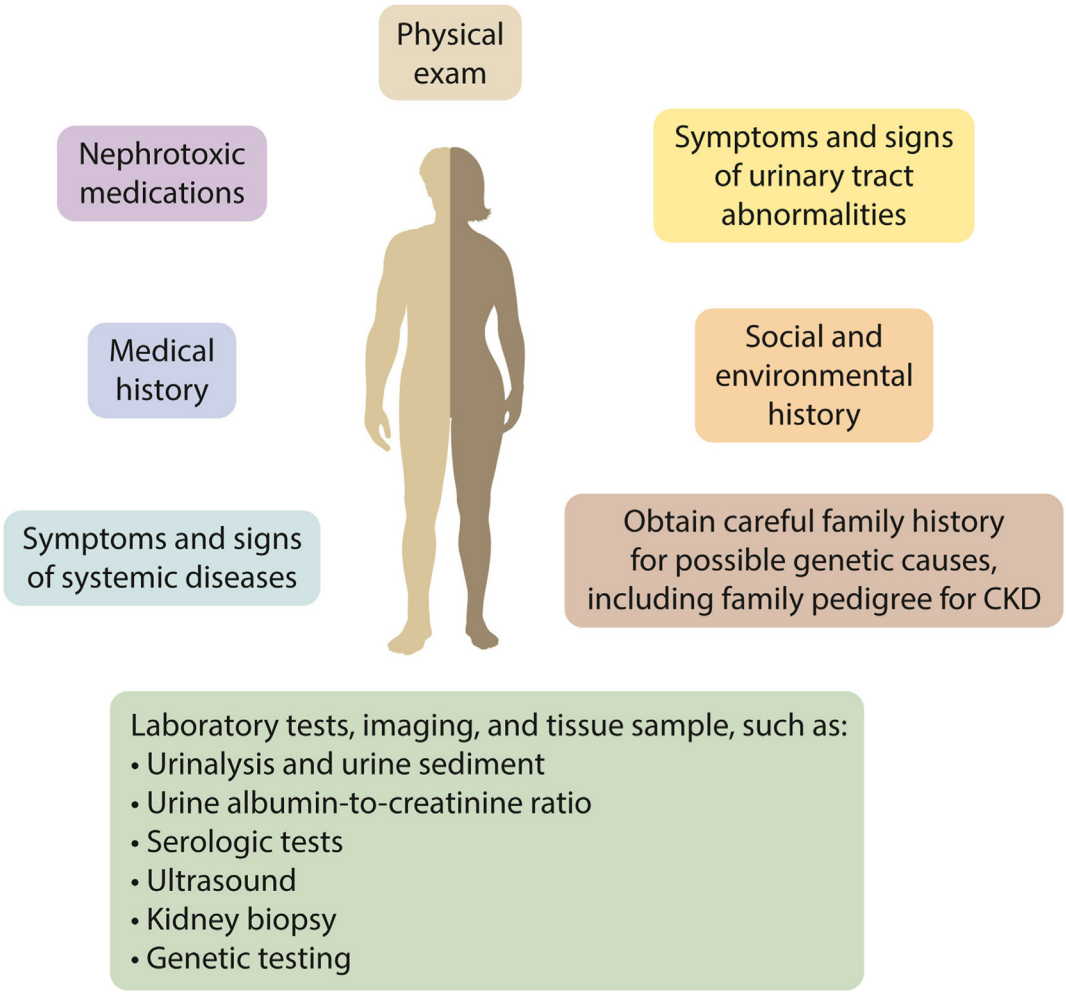

Figure 1. Evaluation of cause of CKD. Image ©2024 KDIGO; reproduced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024 Apr;105(4S):S117-S314[23] with permission of the copyright holder.

Commentary and Clinical Utility

Informed by recent evidence and multidisciplinary expert panels convened in 2019 and in 2022 for the KDIGO Controversies Conferences entitled "Early Identification and Intervention in CKD" and "Improving CKD Quality of Care: Trends and Perspectives,"[12,13] chapter 1 relies on the premise that CKD detection meets the World Health Organization (WHO) principles of disease screening.[14,15] Low-cost, accurate diagnostic tests for CKD are available, and early detection of CKD has important implications for lifestyle changes and the growing list of CKD-specific therapies. The current KDIGO guidelines provide several updated practice points related to CKD detection.

Consistent with prior studies, an analysis of over 27 million individuals across 114 international cohorts in the CKD Prognosis Consortium highlighted the graded and additive associations of lower estimated glomerular filtration rate (eGFR) and higher albuminuria with 10 important cardiovascular and kidney outcomes.[16] Based on these findings and implications of eGFR and urinary albumin-creatinine ratio (UACR) results for CKD screening and management, the KDOQI Work Group agrees with the practice points that endorse both UACR and eGFR for CKD testing, with confirmatory repeat testing in those found incidentally to have elevated UACR or low eGFR. While we agree that cystatin C should be combined with Scr to provide the most reliable estimation of GFR, many practitioners may not have access to reliable and timely cystatin C results. If these results are readily available to impact critical medical (eg, CKD diagnosis) or medication-related decision making, both Scr (cr) and cystatin C (cys) should be obtained at the same time and used to estimate the GFR ($eGFR_{cr\text{-}cys}$).

In the absence of US Preventive Services Task Force recommendations regarding CKD screening in nondiabetic populations as well as the lack of trial-level evidence for specific CKD-detection strategies within the United States, the persistent workforce shortages in both general

medicine and nephrology, and the increased health system costs, we also agree with prioritizing CKD screening or detection among those with hypertension, diabetes, and CVD. This targeted approach focuses on the most common CKD risk factors within the United States, includes individuals with conditions (ie, hypertension and CVD) that represent a substantial opportunity for CKD detection and thus intervention,[17] and aligns well with the growing movement toward integration of CKD detection and treatment with other chronic conditions such as diabetes and CVD.[18] For individuals who have preserved kidney function, further studies are needed to determine the optimal CKD screening interval that balances case detection with workforce burden and cost considerations. In light of the current dearth of data to inform retesting efforts, an individualized approach based on the clinical context seems prudent. Once CKD is detected, the KDOQI Work Group also endorses pursuing a comprehensive workup utilizing an individual's clinical history; behavioral exposures; social determinants of health;[19,20] environmental exposures;[21,22] physical findings; and targeted laboratory, genetic, radiologic and histopathologic testing.

The KDIGO guidelines briefly acknowledge the controversy surrounding CKD detection efforts in older adults. Although the aforementioned CKD Prognosis Consortium analyses[16] showed that the relative risks associated with higher albuminuria and lower eGFR were generally weaker in adults aged 65 or older, the absolute risks are much greater in this age group compared with younger age groups. Moreover, studies to date imply that new therapies such as sodium/glucose cotransporter 2 (SGLT2) inhibitors are as effective in reducing cardiovascular events and CKD progression and have similar risk profiles in older adults as in younger adults.[23] The KDOQI Work Group agrees with an individualized approach toward CKD testing in older adults, taking into account the individual patient's risk of progression to kidney failure relative to death;[24] however, we also advocate for additional studies to inform which older adults would benefit from CKD detection and subsequent treatment.

Evaluation of GFR

1.2.1 Other Functions of kidney besides GFR

Practice Point 1.2.1.1. Use the term "GFR" when referring to the specific kidney function of glomerular filtration. Use the more general term "kidney function(s)" when dealing with the totality of functions of the kidney.

Commentary and Clinical Utility

The KDOQI Work Group also acknowledges that GFR represents a single aspect of the kidneys' varied functions and agree with the movement toward using the term "kidney function" to encompass the entirety of kidney health and "GFR" specifying the glomerular filtration capacity of the kidneys. However, in the context of GFR decline, the additional functions of the kidneys are typically affected. While concerted efforts must be made to clarify these additional functions that are distinct from GFR, both estimation of GFR and assessment of UACR remain the most clinically relevant and practical approaches for initial assessment of kidney disease and function decline.

1.2.2 Guidance to physicians and other health care providers

Practice Point 1.2.2.1: Use serum creatinine (SCr) and an estimating equation for initial assessment of GFR.

Recommendation 1.2.2.1: We recommend using eGFRcr-cys in clinical situations when eGFRcr is less accurate and GFR affects clinical decision-making (original guideline Table 8) (1C).

Practice Point 1.2.2.2: Where more accurate ascertainment of GFR will impact treatment decisions, measure GFR using plasma or urinary clearance of an exogenous filtration marker.

Practice Point 1.2.2.3: Understand the value and limitations in both eGFR and measured glomerular filtration rate (mGFR) as well as the variability and factors that influence SCr and cystatin C measurements.

Practice Point 1.2.2.4: Interpretation of SCr level requires consideration of dietary intake.

Practice Point 1.2.2.5: Assess the potential for error in eGFR when assessing change in GFR over time.

Practice Point 1.2.2.6: Consider the use of cystatin C-based estimated glomerular filtration rate (eGFRcys) in some specific circumstances.

Practice Point 1.2.2.7: Understand the implications of differences between eGFRcr and eGFRcys, as these may be informative, in both direction and magnitude of those differences.

Practice Point 1.2.2.8: Consider timed urine collections for measured creatinine clearance if mGFR is not available and eGFRcr-cys is thought to be inaccurate.

Commentary and Clinical Utility

The Work Group supports the KDIGO guidelines' emphasis on the need for clinical providers to understand the degree of variability and the potential biologic and analytic sources of variability for both eGFR and measured GFR. Such understanding supports selection of the most appropriate GFR equation based on patients' clinical characteristics and in the interpretation of results. For the majority of adults without conditions that affect Scr levels independent of GFR, a creatinine-based estimate of GFR ($eGFR_{cr}$) is a reasonable approach for initial evaluation of GFR. For the subset of adults with conditions associated with increased or decreased creatinine generation or impaired tubular secretion that renders $eGFR_{cr}$ unreliable, we agree with the recommendation to use a combined creatinine and cystatin C approach to estimate GFR for CKD screening or confirmation. A recent analysis of data from 4,050 adults from 12 cohorts with measured GFR

demonstrated that the combined creatinine and cystatin C CKD-EPI eGFR equation ($eGFR_{cr-cys}$) yielded more accurate GFR estimates overall and among persons with large discordances between $eGFR_{cr}$ and cystatin C–based eGFR ($eGFR_{cys}$).[25] Although this study used data from study cohorts who were sufficiently healthy to volunteer for a research study, its results may be sufficient for use in other clinical conditions for routine evaluation (Table 1). There remain instances when even a combined $eGFR_{cr-cys}$ may still be inaccurate owing to challenges related to radical differences in body composition or high rates of inflammation and catabolism (eg, advanced cirrhosis or cancer with high cell turnover) or in whom a more precise GFR estimation is needed for critical clinical decision making (eg, kidney-cleared chemotherapeutic agents). The KDOQI Work Group agrees that in these instances timed urine collection or measured GFR (mGFR) by plasma or urinary clearance of radioactive ^{125}I iothalamate or ^{99m}Tc-DTPA or nonradioactive (iohexol) exogenous markers should be used. However, mGFR may be less readily available outside of academic settings, expensive, and cumbersome.

1.2.3 Guidance to clinical laboratories

Practice Point 1.2.3.1. Implement the laboratory standards of care outlined in original guideline Table 11 to ensure accuracy and reliability when assessing GFR using creatinine and cystatin C.

Practice Point 1.2.3.2: Given available resources, clinical laboratories may consider the possibility of measurement of both creatinine and cystatin either as an in-house test or as a referred test.

Special considerations

Pediatric considerations

Practice Point 1.2.3.3: Laboratories measuring creatinine in infants or small children must ensure their quality control process include the lowest end of the expected range of values for the group of interest.

Practice Point 1.2.3.4: Consider the consistent use of enzymatic creatinine assays in children, given the higher relative contribution of non-creatinine chromogens to measured creatinine in children when using the Jaffe assay, and the high prevalence of icteric and hemolyzed samples in the neonatal period.

Practice Point 1.2.3.5: An eGFRcr level <90 ml/min per 1.73 m^2 can be flagged as "low" in children and adolescents over the age of 2 years.

Commentary and Clinical Utility

The KDOQI Work Group supports the laboratory standards of care put forth in Practice Point 1.2.3.1, particularly with using filtration marker assays calibrated to international standard reference materials and reporting eGFR alongside filtration marker concentrations. Like Scr measurements, certified reference materials (ERM-DA471/IFCC) now exist for cystatin C which enable manufacturers to trace their methods to the reference material. A recent assessment by the College of American Pathologists (CAP) of cystatin C assays reported coefficients of variations below 10%, biases below 0.9%, and improved agreement of results across manufacturers.[37]

1.2.4 Selection of GFR estimating equations

Recommendation 1.2.4.1: We recommend using a validated GFR estimating equation to derive GFR from serum filtration markers (eGFR) rather than relying on the serum filtration markers alone (1D).

Practice Point 1.2.4.1: Use the same equation within geographical regions (as defined locally [e.g., continent, country, region] and as large as possible). Within such regions, equations may differ for adults and children.

Practice Point 1.2.4.2: Use of race in the computation of eGFR should be avoided.

Special considerations

Pediatric considerations

Practice Point 1.2.4.3: Estimate GFR in children using validated equations that have been developed or validated in comparable populations.

Commentary and Clinical Utility

The KDOQI Work Group agrees with the KDIGO recommendation to use a GFR estimating equation that has been validated rather than simply rely on the filtration markers alone. Several GFR estimating equations have been developed, most notably the race-free 2021 CKD-EPI GFR estimating equations for creatinine and combined creatinine and cystatin C[38] as well as the European Kidney Function Consortium (EKFC) equations for creatinine, cystatin C, and combined creatinine and cystatin C.[39,40] A large study examining the utility of differences in creatinine-based equations reported that the equations generally perform similarly. However, there were larger regional differences in creatinine-based equations, suggesting the influence of non-GFR determinants of Scr. The differential performance across age, sex, and racial subgroups of creatinine-based GFR equations was attributed to underlying characteristics of the source population from which they were derived.[41] To ensure uniformity within the United States, the KDOQI Work Group supports the use of the race-free 2021 CKD-EPI $eGFR_{cr}$, 2021 CKD-EPI $eGFR_{cr-cys}$, and the 2012 CKD-EPI $eGFR_{cys}$ equations for adults.[38,42,43] These approaches do not include race as a variable in computing or reporting of eGFR and align with the NKF-ASN Task Force recommendations on use of race in diagnosis of kidney disease.[11,44]

As in adult populations, the KDOQI Work Group advocates for use of GFR estimating equations that have been validated in populations with US pediatric participants, as stated in Practice Point 1.2.4.3. The CKiD U25 2021 $eGFR_{cr}$ equation has been developed for individuals aged 1-25 years old with CKD.[45] However, a recent study among young adults aged 18-40 years showed that this equation tends to underestimate GFR at higher levels

whereas the 2021 CKD-EPI $eGFR_{cr}$ equation had minimal bias across GFR levels.[46] Whether GFR estimating equations inclusive of cystatin C could provide improved performance and in which clinical scenarios among the pediatric and young adult population remain to be determined.

The KDIGO guidelines briefly acknowledge the uncertainty of GFR estimation among transgender, nonbinary, and gender-diverse individuals given the lack of studies in this specific population. A study of 258 transgender individuals demonstrated that GFR estimates differed substantially based on the sex coefficient used and varied between those receiving versus not receiving gender-affirming therapy.[47] Given the importance of accurate GFR estimation for decision making, the KDOQI Work Group advocates for additional research to determine how best to assess and monitor kidney function over time in these patient populations. A recently published framework may shed light on the potential path forward.[48]

Evaluation of Albuminuria

1.3.1. Guidance for physicians and other healthcare providers

Practice Point 1.3.1.1: Use the following measurements for initial testing of albuminuria (in descending order of preference). In all cases, a first void in the morning midstream sample is preferred in adults and children.

1. urine ACR, or
2. reagent strip urinalysis for albumin and ACR with automated reading

If measuring urine protein, use the following measurements:

1. urine protein-to-creatinine ratio (PCR),
2. reagent strip urinalysis for total protein with automated reading, or
3. reagent strip urinalysis for total protein with manual reading.

Practice Point 1.3.1.2: Use more accurate methods when albuminuria is detected using less accurate methods.

- Confirm reagent strip positive albuminuria and/or proteinuria by quantitative laboratory measurement and express as a ratio to urine creatinine wherever possible (i.e., quantify the ACR or PCR if initial semi-quantitative tests are positive).
- Confirm ACR ≥30 mg/g (≥3 mg/mmol) on a random untimed urine with a subsequent first morning void in the morning midstream urine sample.

Practice Point 1.3.1.3: Understand factors that may affect interpretation of measurements of urine albumin and urine creatinine and order confirmatory tests as indicated.

Special considerations

Pediatric considerations

Practice Point 1.3.1.4: In children, obtain a first morning urine sample for initial testing of albuminuria and proteinuria (in descending order of preference):

1. Both urine PCR and urine ACR,
2. Reagent strip urinalysis for total protein and for albumin with automated reading, or
3. Reagent strip urinalysis for total protein and for albumin with manual reading.

1.3.2. Guidance to clinical laboratories

Practice Point 1.3.2.1: Implement the laboratory reporting and handling standards outlined in original guideline Table 17 to ensure accuracy and reliability of the findings when assessing urine samples.

Practice Point 1.3.2.2: Implementation of an external quality assessment scheme/program for urine albumin and creatinine, including calculation of the ACR, is a preferred practice for laboratories.

Commentary and Clinical Utility

Given the superior precision and sensitivity of assays for urine albumin compared with urine protein, the KDOQI Work Group agrees with UACR as the preferred method for assessing albuminuria in adults. However, given that most children with CKD have underlying tubular disease, the urinary protein-creatinine ratio (UPCR) is a preferred initial approach for CKD detection in children. While we recognize the rationale for KDIGO guidelines endorsing first morning, midstream void for urine sample collection, the KDOQI Work Group also acknowledges how this may be difficult to implement in real-world practice. The KDOQI Work Group advocates for standardized reporting for UACR (and UPCR) across health systems, comprising of urine albumin, urine creatinine, and the calculated ratio. The variability in urine albumin measurements across methods and clinical laboratories has been well-recognized[49] and limit both detection and monitoring of CKD progression and response to treatment. Therefore, the Work Group also supports working toward quality assurance practices with clinical laboratory adoption of certified reference materials for urine albumin. These efforts will greatly improve clinical interpretation and utilization of UACRs in decision making and provide clinicians with reliable and accurate UACR results.

Point-of-Care Testing

Recommendation 1.4.1: We suggest that point-of-care testing (POCT) may be used for creatinine and urine albumin measurement where access to a laboratory is limited or providing a test at the point-of-care facilitates the clinical pathway *(2C)*.

Practice Point 1.4.1: Whenever a POCT device is used for creatinine and urine albumin testing, ensure that the same preanalytical, analytical, and postanalytical quality criteria relating to the specimen collection and performance of the device, including external quality assessment, and the interpretation of the result is used.

Practice Point 1.4.2: Where a POCT device for creatinine testing is being used, generate an estimate of GFR. Use the equation consistent with that used within the region.

Practice Point 1.4.3: Where a POCT device is being used for albuminuria testing, the capability of also analyzing creatinine and producing an ACR is important. Assess the ability of the POCT ACR devices to produce a positive result in 85% of people with significant albuminuria (ACR ≥30 mg/g or ≥3 mg/mmol), as part of the evaluation and consideration of using the device.

Commentary and Clinical Utility

Point-of-care (POC) testing offers the potential to expand CKD screening; therefore, the KDOQI Work Group agrees with POC testing to enable CKD testing in areas wherein it would otherwise be infeasible, such as in rural areas with limited availability of clinical laboratories, or to facilitate initiation of CKD care as in primary care clinics.[50] Other countries have shown that it is feasible to conduct CKD testing in community pharmacies, which may facilitate detection in high-risk patients.[51,52] The NKF is conducting a pilot study in 3 Missouri community pharmacies. Currently, only Scr is available as a POC test; caution should be exercised when interpreting POC $eGFR_{cr}$ estimates in individuals in whom Scr may not correlate with GFR due to non-GFR effects on creatinine such as tubular secretion. The KDOQI Work Group agrees that POC testing is only useful when the highest test accuracy and precision and the lowest bias can be ensured through appropriate specimen collection and device performance; however, the manufacturers of these devices do not generally report data on their accuracy or reliability. The KDOQI Work Group advocates for reporting the accuracy and precision data for newly developed POC testing devices.

Implementation and Challenges

A study of 24 health care organizations across the United States has previously shown that eGFR testing rates among persons with type 2 diabetes is generally high, with a median percentile testing rate of approximately 90%.[53] In marked contrast, the median percentile testing rate for UACR in these same organizations was 53%. Moreover, the testing rate widely varied across clinical practice sites within each health care organization. A recent analysis of clinical data among persons with diabetes or hypertension across US health care organizations from the Optum 5PCT Database estimated that nearly two-thirds of patients likely to have albuminuria go undetected due to lack of UACR testing.[17] Heterogeneity across health systems in how eGFR and albuminuria results are reported further hinders the clinical utility of these tests. For example, in some health systems, Scr or cystatin C results are reported without the corresponding eGFR. In other instances, urine albumin and creatinine values are reported separately with unclear units of measurement, and the ratio has to be manually calculated by clinical providers. Furthermore, urine albumin is commonly measured without a concurrent urine creatinine. These results reflect the ongoing challenges of CKD detection efforts, particularly with adoption of UACR testing.

In the United States, a number of specific barriers persist that limit the ability of health care providers to include cystatin C measurement in their clinical evaluation. First, although the 2024 Medicare reimbursement rate for cystatin C is 3 times greater than for Scr and 2-fold greater than for a renal function panel,[54] there is no Medicare National Coverage Determination for the use of cystatin C as a method of screening and surveillance of GFR decline. Consequently, this leads to variability in Local Coverage Determination and uncertainty regarding laboratory reimbursement.[55,56] Second, cystatin C testing is not integrated into routine basic or comprehensive metabolic profile tests, and often providers must calculate $eGFR_{cr\text{-}cys}$ on their own. Third, cystatin C availability across US clinical laboratories remains substantially lower than that of Scr.[57] However, the current landscape on the ability to integrate cystatin C into clinical decision making is evolving, with the number of US clinical laboratories offering cystatin C testing steadily increasing over the last 2 years. The increased awareness and test availability of cystatin C may drive associated costs down.[58]

At a general level, multilevel barriers to improving CKD detection persist, including low awareness of CKD in the general public, knowledge gap of CKD detection and interpretation of laboratory results among frontline providers, overburdened clinical providers and health systems, and relative lack of financial and regulatory incentives for providers and health systems to prioritize CKD testing (Table 2).[59-61] Therefore, improving CKD detection and subsequent treatment will require a multipronged approach that comprises patient and provider CKD education and use of technology to lower barriers for CKD testing. Of particular importance are the improvement of awareness of hypertension, CVD, and acute kidney injury (AKI) as other high-risk groups requiring CKD testing and

Table 1. Selected Examples of Conditions Under Which Kidney Function Assessment Using $eGFR_{cr\text{-}cys}$ Should Be Considered for Routine Evaluation but Not Treatment Decision

Condition	Individual Clinical Condition
Expected difference in body composition from participant data used eGFR derivation	• Spinal cord injury with paraplegia/paraparesis or quadriplegia/quadriparesis in the setting of comorbid illness[26] • Above the knee amputation[27] • Severe obesity classified as a body mass index > 40 in adults over the age of 20
Chronic illness	• Cancer[28-31] • Heart failure[32,33] • Cirrhosis[34,35] • Highly catabolic disease states • Muscle-wasting diseases[36]

Measured glomerular filtration rate (mGFR) should be used for treatment decision making. Abbreviations: cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate.

Table 2. Anticipated Barriers to CKD Detection and Treatment

Level	Barriers
Patient	• Low awareness of kidney disease risk or diagnosis • Inability to afford recommended CKD testing and treatment • Low health literacy and numeracy
Provider	• Lack of awareness or confusion surrounding CKD guidelines • Lack of familiarity and understanding of implications of test results for kidney disease, including diagnostic genetic results • Difficulty in managing several CKD risk factors and navigating conflicting treatment goals from different specialists • Competing clinical priorities during clinic visits with individual patients • Belief that they are unable to improve CKD
System	• Limited visit time to care for complex patients • Lack of comprehensive clinical information for chronic disease management • Insufficient clinical support tools and resources to support providers and patients

Abbreviation: CKD, chronic kidney disease.

targeted education on the use and interpretation of UACR and eGFR results.

Rural–urban health care disparities are well-recognized, with the great majority of US counties having few primary care providers available in the rural areas and even fewer specialty care providers.[62,63] This shortage of primary care providers in rural areas is critical because they often serve as the frontline providers for CKD testing in high-risk groups as well as initiate and coordinate specialty care when needed. POC kidney testing at rural community clinics could provide access to kidney testing where primary care is available; emerging tools and services that enable CKD testing at home could broaden access to kidney testing in these remote areas.

Programs such as the NKF's CKDintercept, which tackles several levels of barriers, are imperative in improving CKD detection.[64] At the national level, payer and health system incentives to improve CKD testing among persons with diabetes have recently been established. CKDintercept's Kidney Health Evaluation for patients with diabetes was added as a Healthcare Effectiveness Data and Information Set (HEDIS) measure and is now part of the Centers for Medicare and Medicaid's Medicare Merit-based Incentive Payment System (MIPS).[65,66] At the community level, CKDintercept's "Ending Disparities in CKD" leadership summits have leveraged the collective impact model to engage hundreds of health care and community leaders in discussions regarding the gaps in CKD and the imperative to address them.[67,68] At the individual health system level, CKD testing order sets (eg, the kidney profile) comprising Scr/eGFR$_{cr}$, UACR, and, if indicated and available, cystatin C/eGFR$_{cys}$ as well as automated reporting of UACR and eGFR results concurrently with their individual components are attainable steps toward improving CKD screening.

Kidney screening will likely have limited impact without collaboration between primary care providers and nephrologists to facilitate the interpretation of results and development of individualized treatment plans. Even pragmatic trials of electronic health record (EHR)-based clinical decision support tools for CKD testing and treatment have yielded mixed results.[69,70] Practice facilitation by deployment of allied health professionals and/or population health interventions may increase the bandwidth of clinical providers to sufficiently advance CKD care from diagnosis to treatment.[71,72] However, recent trials with practice-based facilitators or pharmacy-generated EHR alerts have had minimal impact on improving adherence to guideline-based CKD care or improving clinical outcomes.[73,74] The more holistic approach to CKD, cardiovascular and metabolic conditions, and an emphasis on early detection of these conditions recently endorsed by the American Heart Association (AHA) is a highly promising next step and highlights CKD as an important risk factor for CVD.[18]

Although the KDIGO Work Group has primarily focused on CKD screening, we acknowledge that diagnostic workup for those found to have CKD will increasingly involve genetic testing among other routine clinical assessments.[75,76] Further integration of genetic testing into the diagnostic workup for kidney disease will require addressing the availability and affordability of genetic tests, providing education to both primary care and nephrology providers, and establishing resources such as genetic counseling.

Risk Assessment in People with CKD

Overview on Monitoring for Progression of CKD Based Upon GFR and ACR Categories

Practice Point 2.1.1: Assess albuminuria in adults, or albuminuria/proteinuria in children, and GFR at least annually in people with CKD.

Practice Point 2.1.2: Assess albuminuria and GFR more often for individuals at higher risk of CKD progression when measurement will impact therapeutic decisions.

Practice Point 2.1.3: For people with CKD, a change in eGFR of >20% on a subsequent test exceeds the expected variability and warrants evaluation.

Practice Point 2.1.4: Among people with CKD who initiate hemodynamically active therapies, GFR reductions of >30% on subsequent testing exceed the expected variability and warrant evaluation.

Practice Point 2.1.5: For albuminuria monitoring of people with CKD, a doubling of the ACR on a subsequent test exceeds laboratory variability and warrants evaluation.

Commentary and Clinical Utility

Chapter 2 of the KDIGO guideline addresses key principles in assessing risk in CKD through 1 recommendation and several practice points that emphasize the importance of monitoring progression of CKD at least annually using

both eGFR and UACR. This chapter reports that more frequent eGFR and UACR monitoring may be needed in those with higher risk of CKD progression and outlines when eGFR and UACR measurement will impact therapeutic decisions (Fig 2). It is important to note that UACR levels can vary substantially. Thus, a practice point suggests that a doubling of the UACR may exceed expected variability and warrant evaluation. The KDOQI Work Group emphasizes the need to individualize the frequency of UACR testing depending on several factors, such as the etiology of disease, the therapeutic regimen that may be intensified based on albuminuria, disease etiology, and the baseline UACR level. For example, residual albuminuria detected while on an appropriately dosed renin angiotensin system (RAS) inhibitor and SGLT2 inhibitors should prompt a clinician to consider adding a nonsteroidal mineralocorticoid receptor antagonist in a patient with type 2 diabetes. In addition, the American Diabetes Association (ADA) standards of care recommend for people with diabetes and ACR ≥ 300 mg/g reducing ACR by 30% or greater to slow CKD progression.[77]

Variability in eGFR was also addressed by KDIGO with a practice point suggesting that a change in eGFR of >20% on a subsequent test exceeds the expected variability and warrants evaluation. However, if a hemodynamically active therapy is initiated (eg, RAS inhibitors or SGLT2 inhibitors), a threshold of >30% is suggested to exceed the expected variability and warrant further evaluation. Post hoc analyses examining outcomes by initial eGFR decreases after SGLT2 inhibitors have shown that individuals with initial eGFR decreases of >10% have similar eGFR trajectories and long-term kidney benefits as those with an initial eGFR decrease of ≤10%.[78,79] Treatment with diuretics may increase the risk of an eGFR dip with SGLT2 inhibitors. Initial eGFR declines of >30% are rare and should warrant review of volume status, blood pressure (BP), and other causes, as well as

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 2. Frequency of monitoring glomerular filtrate rate (GFR) and albuminuria in people with chronic kidney disease (CKD). Albuminuria and GFR grid reflects the risk of progression by intensity of coloring (green, yellow, orange, red, and deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Image ©2024 KDIGO; reproduced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314[23] with permission of the copyright holder.

repeat testing. Among individuals in the EMPA-REG trial (eGFR ≥ 30 mL/min/1.73 m^2 and no ACR requirement) who experienced a >30% eGFR initial dip after starting SGLT2 inhibitors, eGFR stabilized without further decline after 12 weeks. In the CREDENCE trial (eGFR 30-89 and ACR 300-5,000 mg/g), the long-term eGFR trajectory was similar to the main analyses although these individuals had higher adverse events during prolonged treatment, which warrants careful evaluation and monitoring.[78,79] Hemodynamic-related declines in eGFR may also occur with RAS inhibitors[80,81] and with initiation of both nonsteroidal and steroidal mineralocorticoid receptor antagonists.[3,82] Cardiovascular and CKD outcomes in 2 clinical trials that studied the effects of finerenone, a nonsteroidal mineralocorticoid receptor antagonist, versus placebo with concurrent RAS inhibitor therapy (FIGARO and FIDELIO) were similar between SGLT2 inhibitor users and nonusers.[3,8,83] However, the data remain limited on the effect of combining SGLT2 inhibitors with mineralocorticoid receptor antagonists on background RAS inhibitor therapy. A randomized crossover trial found that dapagliflozin-eplerenone had robust additive albuminuria-lowering effects, accompanied by a reversible eGFR initial dip. Future studies will need to determine the long-term CKD and cardiovascular outcomes with dual SGLT2 inhibitors and mineralocorticoid receptor antagonist treatment.[84]

Implementation and Challenges

Large gaps in albuminuria testing remain among patients at risk for or diagnosed with CKD, as discussed earlier in chapter 1.[17,85] Barriers to albuminuria testing include limited education on CKD, low awareness of CKD by patients, lack of understanding of the importance of testing and its interpretation, and limited CKD guidelines awareness among non-nephrologists. Health care system limitations such as inadequate, disparate access to care, lack of a streamlined interface between resultant laboratory and additional next-step testing, and various limitations of EHRs add to the barriers to testing.[59,86] Often there can be difficulty in obtaining a urine sample at a clinic visit; 1 quality improvement study found that use of an EHR dashboard by clinic staff allowed the clinic staff to "pend" electronic orders and increase albuminuria testing.[87] Other interventions that could address albuminuria screening include using electronic alerts with the risk of alert fatigue and use of home-based testing for albuminuria.[88,89]

Risk Prediction in People With CKD

Recommendation 2.2.1: In people with CKD G3–G5, we recommend using an externally validated risk equation to estimate the absolute risk of kidney failure *(1A)*.

Practice Point 2.2.1: A 5-year kidney failure risk of 3%–5% can be used to determine need for nephrology referral in addition to criteria based on eGFR or urine ACR, and other clinical considerations.

Practice Point 2.2.2: A 2-year kidney failure risk of >10% can be used to determine the timing of multidisciplinary care in addition to eGFR-based criteria and other clinical considerations.

Practice Point 2.2.3: A 2-year kidney failure risk threshold of >40% can be used to determine the modality education, timing of preparation for kidney replacement therapy (KRT) including vascular access planning or referral for transplantation, in addition to eGFR-based criteria and other clinical considerations.

Practice Point 2.2.4: Note that risk prediction equations developed for use in people with CKD G3–G5, may not be valid for use in those with CKD G1–G2.

Practice Point 2.2.5: Use disease-specific, externally validated prediction equations in people with immunoglobulin A nephropathy (IgAN) and autosomal dominant polycystic kidney disease (ADPKD).

Prediction of Cardiovascular Risk in People With CKD

Practice Point 2.3.1: For cardiovascular risk prediction to guide preventive therapies in people with CKD, use externally validated models that are either developed within CKD populations or that incorporate eGFR and albuminuria.

Practice Point 2.3.2: For mortality risk prediction to guide discussions about goals of care, use externally validated models that predict all-cause mortality specifically developed in the CKD population.

Commentary and Clinical Utility

Recommendation 2.2.1 emphasizes the need to use individualized risk prediction to personalize CKD care. Several models are highlighted, such as the Kidney Function Risk Equation (KFRE),[90] which provides 2-year and 5-year risk estimates for kidney failure and has been validated in >1 million individuals in >60 cohorts. Importantly, KFRE includes routinely measured laboratory values (4-variable age, sex, eGFR, and UACR; 8-variable adds calcium, phosphate, bicarbonate, and albumin) and can potentially be incorporated into the EHR and laboratory reporting. External validation is immensely important because algorithms can have good discrimination but suboptimal calibration (difference between observed and predicted risk), resulting in systematically biased predicted risk estimates that are too high or too low. When possible, local calibration may be helpful. For example, a regional calibration factor improved calibration of the KFRE for non–North American cohorts.[90] Risk scores incorporating additional variables such as cystatin C (Z6 score) may be useful depending on availability of cystatin C testing in the future and additional validation outside of Europe.[91]

The guidelines stress the importance of using appropriate risk prediction models that are externally validated

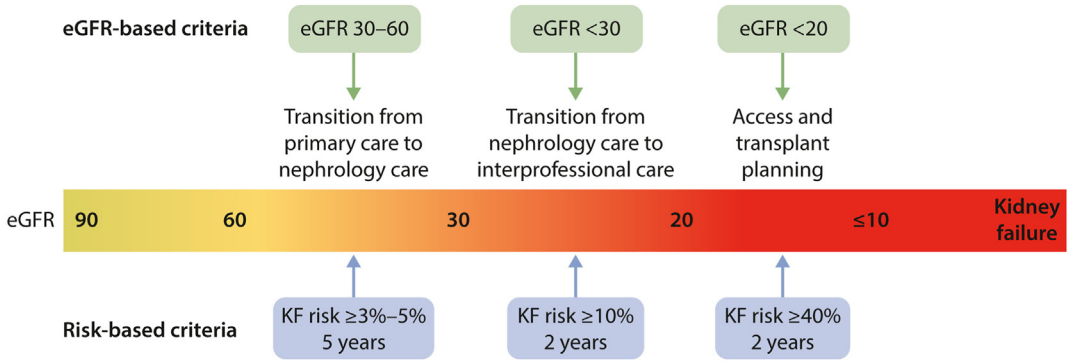

Figure 3. Transition from an estimated glomerular filtration rate (eGFR)-based to a risk-based approach to chronic kidney disease care. Image ©2024 KDIGO; reproduced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314[23] with permission of the copyright holder.

and for disease-specific predictions. For example, KFRE was developed in adults with stages G3-G5 CKD. Thus, other externally validated equations should be considered for evaluating CKD risks for patients with stages G1-G2 CKD.[92-94] Externally validated models that have included individuals without baseline CKD include a model developed by the CKD Prognosis Consortium to predict incident CKD[95] and proprietary models such as Klinrisk and KidneyIntelx that incorporate additional laboratory features to predict risk of kidney failure.[93,96] A risk calculator exists for children with CKD using data from Chronic Kidney Disease in Children (CKiD) to estimate time to kidney replacement therapy in pediatric patients.[97] Disease-specific equations may incorporate other variables more specific to their conditions such as risk prediction tools for autosomal dominant polycystic kidney disease[98,99] and IgA nephropathy.[100,101]

To estimate risk, KDIGO also provides practice points for thresholds of predicted kidney failure risk, such as 5-year kidney failure risk of ≥3%-5% to inform nephrology referral, 2-year kidney failure risk of ≥10% for transitioning to interprofessional care, and 2-year kidney failure risk of ≥40% for access and transplant planning (Fig 3). The KDOQI Work Group agrees that incorporation of validated risk equations into clinical care could be helpful in providing individualized care, and the KDOQI 2019 Vascular Access guidelines recommend a risk-based threshold of >50% 2-year risk of kidney failure or eGFR < 15 mL/min/1.73 m^2 based on expert opinion.[102]

Practice points also discuss cardiovascular risk prediction, stating the need to use models developed within CKD populations or that incorporate eGFR and albuminuria. As patients with CKD are at exceptionally high risk of CVD, absolute risk may be underestimated in patients with CKD using traditional risk prediction tools such as the Atherosclerotic Pooled Cohort Equation.[103] The new American Heart Association Predicting Risk of CVD Events (AHA PREVENT) equation now incorporates eGFR into risk estimation in the base model and provides a much improved calibrated CVD risk prediction.[104] Additional AHA PREVENT equations add variables including UACR, hemoglobin A_{1c}, and social deprivation index. Adding UACR to the base model substantially improves calibration in patients with UACR > 300 mg/g. Similarly, mortality risk prediction tools should use models developed in CKD populations to promote discussions about conservative care pathways. An example of this is the CKD Prognosis Consortium, which uses Markov processes with Monte Carlo simulations to predict probability and timing of kidney failure, CVD, and death.[105]

Implementation and Challenges

The concept of using KFRE ≥10% to guide access to interprofessional care comes primarily from experiences in Canada, where qualifying patients receive care from a team that includes a nurse case manager, dietitian, pharmacist, and social worker.[106-108] A mixed methods study evaluating this risk-based approach to multidisciplinary CKD care found that most patients and providers felt this approach allowed targeting of the highest-risk patients with similar provider job satisfaction after KFRE implementation.[108] However, some providers expressed concern about the KFRE's accuracy and the impact on care for low-risk patients. Similar concerns have been raised in US studies. In a pragmatic, randomized clinical trial, clinical decision support incorporating a noninterruptive KFRE alert at the point of care to primary care clinics did not improve stage-appropriate monitoring or nephrology referral.[69] Lack of familiarity with KFRE among primary care providers was a major concern. Challenges also exist for implementation of KFRE into nephrology clinics. After implementation of KFRE into an EHR, a US nephrology clinic reported uneven uptake in use of KFRE among nephrologists (3 documented KFRE in >75% of notes, 25 documented KFRE in <10% of notes).[109] Collectively, these studies

suggest there is a need for increasing education of providers and patients in order to improve utility of KFRE implementation into clinical care.

Challenges to implementing the Canadian interdisciplinary model based on KFRE thresholds include limited access to health care (eg, nephrologists, dietitians, pharmacists) and scheduling challenges. These problems are compounded in rural, underserved areas and for solo practitioners. Opportunities exist in advancing new innovative models to test out team-based approaches to care for patients with high KFRE risk.[110] However, there is a need for substantial EHR information technology support to implement risk scores and for education of patients, primary care providers, and nephrologists to ensure success. Finally, population health approaches to determining access to care (eg, above a specific KFRE risk threshold) and related policies should be intermittently reviewed to ensure there is no unintended harm given the imprecision of these predictions.

Delaying CKD Progression and Managing Its Complications

CKD Treatment and Risk Modification

Practice Point 3.1.1: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications.

Commentary and Clinical Utility

This subsection of the chapter provides basic guidelines to support holistic management of the risks associated with CKD, mostly in line with previously published KDIGO clinical practice guidelines.[111,112] A very useful figure, especially for primary care physicians, is provided for the stepwise approach to guide management of kidney disease and associated CVD (Fig 4). CKD imparts adverse consequences on fertility and pregnancy outcomes; these issues are briefly discussed in this section, and their implications for clinical practice (beyond close monitoring and counseling) in the absence of robust evidence is not clear.

Lifestyle Factors

Practice Point 3.2.1: Encourage people with CKD to undertake physical activity compatible with cardiovascular health, tolerance, and level of frailty; achieve an optimal body mass index (BMI); and not use tobacco products. Referral to providers and programs (e.g., psychologists, renal dietitians or accredited nutrition providers, pharmacists, physical and occupational therapy, and smoking cessation programs) should be offered where indicated and available.

3.2.2. **Physical activity and optimum weight**

The KDOQI Work Group concurs with all the recommendation and practice points relating to physical activity from the "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease"[111] and the "KDOQI US Commentary on the KDIGO 2020 Clinical Practice Guidelines for Diabetes Management in CKD"[113] and consider that they should extend to all adults with CKD.

Recommendation 3.2.2.1: We recommend that people with CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (1D).

Practice Point 3.2.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.

Practice Point 3.2.2.2: People with CKD should be advised to avoid sedentary behavior.

Practice Point 3.2.2.3: For people at higher risk of falls, healthcare providers should provide advice on the intensity of physical activity (low, moderate, or vigorous) and the type of exercises (aerobic vs. resistance, or both).

Practice Point 3.2.2.4: Physicians should consider advising/encouraging people with obesity and CKD to lose weight.

Special considerations

Pediatric considerations

Practice Point 3.2.2.5: Encourage children with CKD to undertake physical activity aiming for World Health Organization (WHO)-advised levels (i.e., ≥60 minutes daily) and to achieve a healthy weight.

Commentary and Clinical Utility

This subsection of the chapter provides guidance on lifestyle factors that are known to impact progression of kidney disease, its complications, and comorbidities. Overall, the KDOQI Work Group agrees with the practice points and recommendations of KDIGO CKD guidelines and the previous "KDOQI US Commentary on the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD"[113] wherein the importance of various lifestyle interventions is discussed in detail. Avoidance of tobacco products to minimize CVD, respiratory disease, and cancer risks is appropriately noted. In the KDIGO CKD guidelines, the emphasis on physical activity and weight management is commendable although the reference to "optimal" weight could result in some uncertainty and confusion in different patient endotypes. For example, the mortality risk associated with BMI and weight differs with increasing age and stage of kidney disease.[114] A more preferred wording could be "weight within range appropriate for age, gender, and comorbidities."

Implementation and Challenges

Important barriers to the implementation of lifestyle recommendations is the psychosocial, socioeconomic, and behavioral factors related to the patient population and the intended modifications.[115] A recommendation of 150 minutes per week of moderate-intensity physical

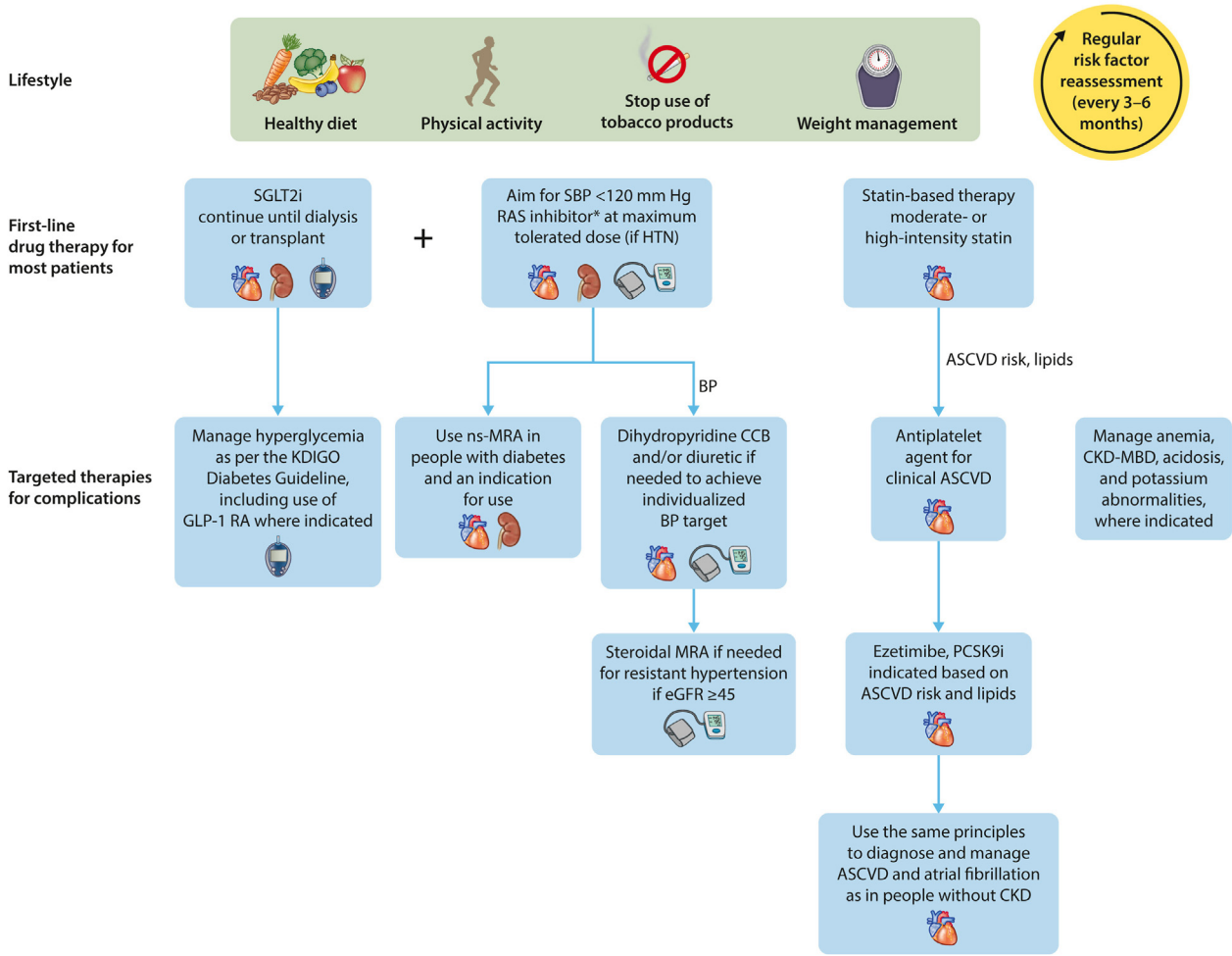

Figure 4. Holistic approach to chronic kidney disease (CKD) treatment and risk modification. *Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be first-line therapy for blood pressure (BP) control when albuminuria is present; otherwise dihydropyridine calcium channel blocker or diuretic can also be considered. All 3 classes are often needed to attain BP targets. Icons presented indicate the following benefits: blood pressure cuff = blood pressure–lowering; glucometer = glucose-lowering; heart = heart protection; kidney = kidney protection; scale = weight management. ASCVD, atherosclerotic cardiovascular disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor. Image ©2024 KDIGO; reproduced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314[23] with permission of the copyright holder.

activity for all patients may not be feasible given the broad demographic and clinical characteristics of the entire CKD patient population.[116] However, the KDOQI Work Group agrees that health care providers should encourage physical activity and exercise as tolerated by the individual patient.

Diet

Practice Point 3.3.1: Advise people with CKD to adopt healthy and diverse diets with a higher consumption of plant-based foods compared to animal-based foods and a lower consumption of ultra-processed foods.

Practice Point 3.3.2: Use renal dietitians or accredited nutrition providers to educate people with CKD about dietary adaptations regarding sodium, phosphorus, potassium, and protein intake, tailored to their individual needs, and severity of CKD and other comorbid conditions.

3.3.1. Protein intake

Recommendation 3.3.1.1: We suggest maintaining a protein intake of 0.8 g/kg body weight/d in adults with CKD G3–G5 *(2C)*.

Practice Point 3.3.1.1: Avoid high protein intake (>1.3 g/kg/d) in adults with CKD at risk of progression.

Practice Point 3.3.1.2: In adults with CKD who are willing and able, and who are at risk of kidney failure, consider prescribing, under close supervision, a very low–protein diet (0.3-0.4 g/kg body weight/d) supplemented with essential amino acids or ketoacid analogs (up to 0.6 g/kg body weight/d).

Practice Point 3.3.1.3: Do not prescribe low- or very low–protein diets in metabolically unstable people with CKD.

Special considerations

Pediatric considerations

Practice Point 3.3.1.4: Do not restrict protein intake in children with CKD due to the risk of growth impairment. The target protein and energy intake in children with CKD G2–G5 should be at the upper end of the normal range for healthy children to promote optimal growth.

Older adults

Practice Point 3.3.1.5: In older adults with underlying conditions such as frailty and sarcopenia, consider higher protein and calorie dietary targets.

3.3.2. Sodium intake

The KDOQI Work Group concurs with the following recommendation from "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease"[111] and the "KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease"[112] and also recommend readers to review the "KDOQI US Commentary on the 2021 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD."[117]

Recommendation 3.3.2.1: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in people with CKD *(2C)*.

Practice Point 3.3.2.1: Dietary sodium restriction is usually no appropriate for patients with sodium-wasting nephropathy.

Special considerations

Pediatric considerations

Practice Point 3.3.2.2: Follow age-based Recommended Daily Intake when counseling about sodium intake for children with CKD who have systolic and/or diastolic blood pressure >90th percentile for age, sex, and height.

Commentary and Clinical Utility

This subsection of the chapter provides guidance on dietary aspects and dietary management in patients with CKD. However, the available dietary guidelines published by other entities were not completely considered for this subsection (nutrition guidelines are referenced in the section discussing potassium), which is a missed opportunity for cross-fertilization between leading guideline-producing entities within the discipline. We endorse that future efforts integrate these various guidelines to facilitate translation into practice.

The overarching practice points 3.3.1 and 3.3.2 about adopting a healthy and diverse diet with an emphasis on food quality and comanagement of the diet with an expert dietitian or accredited nutrition provider are appropriate and provided as practice points due to lack of adequately sized randomized controlled trials.

Subsection 3.3.1 includes the recommendation to maintain a dietary protein intake of 0.8 g/kg per day in adults with CKD G3-G5 (2C), which does not address the current evidence showing the potential beneficial effects of lower levels of dietary protein intake, albeit in controlled settings. The emphasis on practicality and safety of low-protein diets (LPD) and supplemented very-low-protein diets (sVLPD) are commendable although there are no studies showing serious nutritional deficiencies with LPDs or sVLPDs under appropriate supervision. Although reference is made to proper scrutiny of the randomized controlled trials examining LPD and sVLPD, no reference is made to available systematic reviews on the subject.[118] This recommendation does not completely align with other published nutrition guidelines and systematic reviews. For example, the "KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update"[114] recommends a low-protein diet (0.55-0.6 or 0.28-0.43 g/kg per day with keto-acid analogs) should be delivered for nondiabetic and metabolically stable patients with stages 3 and 4 CKD. This should be done under close clinical supervision, preferentially by a dietitian, to reduce any risk that might be associated with decreased nutrient intake. On the other hand, for patients with diabetic kidney disease, a more modest dietary protein restriction is recommended (0.6-0.8 g/kg per day).[114] The conflicting recommendations could be due to the consideration of behaviors that are culturally and socially influenced in different regions worldwide (ie, North America vs Asia, especially the Far East).

Implementation and Challenges

The challenges in implementation of dietary restrictions are appropriately noted in the guideline. However, additional guidance to overcome these challenges are warranted. Additional challenges noted by the KDOQI Work Group include the lack of data to guide various methods to implement various dietary modifications in patients with CKD, especially patients with stages 3-5d. Further, additional discussion regarding psychosocial aspects of dietary modifications and geographical variations in dietary patterns would have been particularly useful in this section. For example, people living in poverty may be more likely to consume ultraprocessed foods, which contain more sodium and phosphorus,

which thus make it difficult to adhere to the guidelines. Finally, fewer than 10% of US adults with CKD ever meet with a dietitian; medical nutrition therapy provides a practical solution to the issues mentioned here because it is covered by Medicare and other private insurers.[119]

Blood Pressure Control

The Work Group concurs with the "KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease"[112] and recommend readers to refer to the "KDOQI US Commentary on the 2021 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD"[117] as we highlight the following guidance.

Recommendation 3.4.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement *(2B)*.

Practice Point 3.4.1: Consider less intensive BP-lowering therapy in people with frailty, high risk of falls, very limited life expectancy, or symptomatic postural hypotension.

Special considerations

Pediatric considerations

Recommendation 3.4.2: We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ambulatory blood pressure monitoring (ABPM) should be lowered to ≤50th percentile for age, sex, and height *(2C)*.

Practice Point 3.4.2: Monitor BP once a year with ABPM and every 3–6 months with standardized auscultatory office BP in children with CKD.

Practice Point 3.4.3: In children with CKD, when ABPM is not available, it is reasonable to target manual auscultatory office SBP, obtained in a protocol-driven standardized setting, of 50th–75th percentile for age, sex, and height unless achieving this target is limited by signs or symptoms of hypotension.

Commentary and Clinical Utility

These recommendations and practice points are similar to those outlined in the previous KDIGO guidelines on management of BP in CKD. Postural hypotension is a common limiting condition for intensive control of BP to <120/70 mm Hg. "Symptomatic postural hypotension" is not necessarily straightforward to ascertain by clinical history alone, especially in elderly and chronically ill patients. Measurement of orthostatic BP and pulse in the clinic for such patients is an important component of the physical examination that warrants attention for clinical decision making at the point of care. The BP guideline also emphasizes that the goal of <120/70 mm Hg is only appropriate with oscillometric BP measured according to AHA protocols. Most US clinics do not measure BP this way, which is an important practical caveat. Moreover, the AHA/ACC and ADA recommend a BP goal of <130/80 mm Hg based on the available evidence for cardiovascular risk reduction. Home BP monitoring is an alternative if clinic BP is not standardized and to avoid overtreating "white coat" hypertension. Thus, the KDOQI Work Group agrees with the lower strength of recommendation for intensive BP reduction in the KDIGO guidelines and the KDOQI commentary published in 2021.[117]

Glycemic Control

Please refer to the "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease"[111] and the "KDOQI Commentary on the KDIGO 2022 Update to the Clinical Practice Guideline for Diabetes Management in CKD"[120] for specific recommendations, practice points, and research recommendations.

Renin Angiotensin System Inhibitors

The Work Group highlights recommendations from the "KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease"[112] and selected practice points for treatment with RAS inhibitors from that guideline and the "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease."[111] Notably, the KDIGO Work Group endorsed several recommendations to apply even in the absence of high BP and have adapted the recommendations from the BP guideline to remove this requirement. Key recommendations and practice points are highlighted here.

Recommendation 3.6.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with CKD and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.

Recommendation 3.6.2: We suggest starting RASi (ACEi or ARB) for people with CKD and moderately increased albuminuria (G1–G4, A2) without diabetes *(2C)*.

Recommendation 3.6.3: We recommend starting RASi (ACEi or ARB) for people with CKD and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes *(1B)*.

Recommendation 3.6.4: We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in people with CKD, with or without diabetes *(1B)*.

Practice Point 3.6.1: RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Practice Point 3.6.2: Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

Practice Point 3.6.3: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

Practice Point 3.6.4: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

Practice Point 3.6.5: Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

Practice Point 3.6.6: Consider starting people with CKD with normal to mildly increased albuminuria (A1) on RASi (ACEi or ARB) for specific indications (e.g., to treat hypertension or heart failure with low ejection fraction).

Practice Point 3.6.7: Continue ACEi or ARB in people with CKD even when the eGFR falls below 30 ml/min per 1.73 m^2.

Commentary and Clinical Utility

These recommendations and practice points for angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use in diabetes and CKD aligns with recommendations from the previous KDIGO guidelines on diabetes and CKD, the ADA-KDIGO consensus statement, and the ADA's "Standards of Care in Diabetes—2024."[77,121] In clinical practice, whether and when RAS inhibitors should be stopped have been a matter of debate. In a clinical trial of ACEI discontinuation versus continuation in patients with CKD and eGFR < 30 mL/min/1.73 m^2, discontinuation had no benefit for preservation of eGFR or prevention of kidney failure accrued over 3 years of follow-up. Persons with either type 1 diabetes or type 2 diabetes had similar results to those without diabetes. Therefore, ACEI discontinuation is not expected to improve eGFR, though maintaining this therapy could have other benefits such as cardiovascular protection even in those with advanced kidney disease.[122,123] Although KDIGO recommendations suggest waiting 2-4 weeks to check BP, Scr, and potassium after RAS inhibitor initiation or dose increase, the 2024 ADA standards of care in diabetes recommend evaluation of these parameters within 1-2 weeks, which is also a reasonable approach.[124] ACEI and ARBs have a rapid effect on glomerular hemodynamics, and the potential for AKI in many high-risk persons with CKD (elderly, on diuretics, SGLT2 inhibitors, mineralocorticoid receptor antagonists, volume depletion, lower GFR) suggests that shorter-term monitoring is warranted in many persons with CKD.

Implementation and Challenges

ACEIs and ARBs remain markedly underutilized in clinical practice despite compelling data supporting their use for more than 3 decades. For example, in the CURE-CKD Registry of real-world data from 2 large US health systems between 2006 and 2017, ACEI/ARB prescribing in CKD overall was 20.6% and 25% in those with CKD and hypertension or diabetes, respectively.[125] Although this number increased to 70.7% in patients with diabetes and CKD by 2019-2020, persistence of ACEI/ARB use fell to 40.4% after just 90 days.[126] Clinical pharmacists focused on comprehensive medication management, hypertension, and diabetes management have demonstrated improvement in ACEI/ARB adherence, control of diabetes and BP, patient and provider satisfaction, reduced hospitalization, and cost savings.[127-132] Multidisciplinary coordinated primary care has also been demonstrated to improve diabetes and BP control and increase ACEI/ARB adherence. A reduction in incidence of kidney failure by 54% between 1996 and 2013 was observed in the American Indian population after the Indian Health Service implemented a population health strategy with primary care–based education, screening, and case management that included a multidisciplinary team of primary care clinicians, nurses, pharmacists, dietitians, and community health workers to improve control of hyperglycemia and hypertension and increase ACEI/ARB use to >70%.[133,134]

Sodium/Glucose Contransporter 2 Inhibitors

Recommndation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

Practice Point 3.7.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:
- eGFR ≥20 ml/min per 1.73 m^2 with urine albumin-to-creatinine ratio (ACR) ≥200 mg/g (≥20 mg/mmol), or
- heart failure, irrespective of level of albuminuria.

Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

Commentary

Following initial signals of kidney protection from cardiovascular outcome trials (CVOTs) with agents from the SGLT2 inhibitor class in type 2 diabetes, 3 dedicated kidney disease outcome trials with canagliflozin, dapagliflozin, and empagliflozin established SGLT2 inhibitors as a first-line standard of care for people with CKD including those

with or without type 2 diabetes.[4-7,9,10] Importantly, all 3 of the kidney disease trials tested SGLT2 inhibitors on top of background therapy with an ACEI or an ARB.

The first kidney disease trial was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), which enrolled participants with type 2 diabetes, eGFR ≥ 30 to < 90 mL/min/1.73 m^2, and severely increased albuminuria (A3). A 30% relative risk reduction for the primary composite outcome (kidney failure defined by dialysis, transplantation, or sustained eGFR < 15 mL/min/1.73 m^2; doubling of Scr; or death from kidney disease) was observed.[7] The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trials included populations with and without type 2 diabetes. Participants had baseline eGFR levels as low as 25 mL/min/1.73 m^2 or 20 mL/min/1.73 m^2 and UACR ≥ 200 mg/g or any amount including none, respectively. Relative risk reductions were 39% in DAPA-CKD and 28% in EMPA-KIDNEY for primary composite outcomes similar to CREDENCE.[4,5] Subgroup analyses from the kidney disease trials found no significant effect modification based on diabetes, baseline eGFR, or other clinical characteristics. Comparable findings were reported by a meta-analysis that included multiple large SGLT2 inhibitor outcome trials from CVOTs and heart failure trials as well as the kidney disease trials.[135]

The KDOQI Work Group concurs with a strong recommendation supporting the use of SGLT2 inhibitors as a first-line agent for kidney and heart protection for those with eGFR ≥ 20 mL/min per 1.73 m^2 and UACR ≥ 200 mg/g (≥20 mg/mmol). In Practice Point 3.7.1, it should be noted that use of SGLT2 inhibitors with proven kidney and cardiovascular benefits should be prioritized over others that have not demonstrated similar benefits. In Practice Point 3.7.3, the lack of trial evidence to date was noted as the main reason for the evidence ranking of "2B" for SGLT2 inhibitors in patients with eGFR 20-45 mL/min/1.73 m^2 and UACR < 200 mg/g. Yet all evidence to date (eg, eGFR slope analyses) suggests potential preservation of GFR over time with SGLT2 inhibitors in those with eGFR 20-45 and UACR < 30 mg/g as well.[5,136]

There is limited evidence to suggest that dapagliflozin is safe to use in persons receiving dialysis.[137] However, the US Food and Drug Administration (FDA) reviewed safety data on dapagliflozin in patients who had initiated dialysis during the DAPA-CKD trial and concluded there were no safety signals. Following this, the statement that dapagliflozin should be discontinued when dialysis was initiated was removed from the package insert. The KDOQI Work Group believes that there is not enough evidence to suggest that these medications are effective in patients receiving kidney replacement therapy.[138] Ongoing trials are exploring the potential benefits of SGLT2 inhibitors in dialysis and transplant patients.[139] Other clinical trials are moving quickly to consider SGLT2 inhibitors as the background standard of care for testing new kidney protective agents for CKD, in some cases irrespective of albuminuria.

Clinical Utility

Several side effects have been reported with SGLT2 inhibitor use. We agree with KDIGO guidelines that risk mitigation strategies for SGLT2 inhibitor side effects should include hygienic counseling to avoid genital mycotic and urinary tract infections, sick day rules and insulin guidance for reducing risk of "normoglycemic" ketoacidosis, and reduction of diuretics for patients at risk for hypovolemia or hypotension (Table 3).[121,140] SGLT2 inhibitor initiation is associated with a reversible decline in eGFR of 3-5 mL/min/1.73 m^2 in the first 4 weeks of therapy. Following this initial "eGFR dip," GFR typically stabilizes during ongoing SGLT2 inhibitor therapy.[78,141]

Because SGLT2 inhibitor therapy reduces blood glucose in persons with preserved eGFR, reduction of insulin or insulin secretagogues may be needed to avoid hypoglycemia in those with eGFR >45 mL/min/1.73 m^2.[121]

Notably, some SGLT2 inhibitor side effects are beneficial. These agents reduce risks of hyperkalemia, without causing hypokalemia, and mitigate fluid retention. Therefore, SGLT2 inhibitors can facilitate initiation and persistent use of other guideline-directed medical therapies such as RAS inhibitors, mineralocorticoid receptor antagonists, and endothelin antagonists, respectively.[142,143]

Implementation and Challenges

As observed for underutilization of ACEI/ARB, only 6.0% of patients with diabetes and CKD were prescribed an SGLT2 inhibitor in the CURE-CKD Registry during the years 2019-2020. Persistent use of an SGLT2 inhibitor for at least 90 days was 5.0%.[126] In patients with commercial health insurance as recently as 2020, SGLT2 inhibitor initiation was reported in just 13% of patients with diabetes and CKD.[144] The US Veterans Administration (VA) health system does not have typical prescribing barriers, yet SGLT2 inhibitors remain underutilized in 2020 with prescriptions for 11.5% of patients with type 2 diabetes, CKD, and atherosclerotic CVD. Disparities in use were seen for women, persons who identify as Black race, and different VA facilities.[145] The current out-of-pocket costs of these agents in the United States limit access for many patients, but it is anticipated that generic dapagliflozin and/or empagliflozin may become available starting in 2025 or 2026.

Similar to the situation with ACEI/ARB, efforts to increase implementation of SGLT2 inhibitors are warranted. The Cardio-Kidney-Metabolic (CKM) initiative from the AHA has promoted recognition of CKD as a major risk CVD enhancer with inclusion of eGFR and UACR in the new PREVENT risk calculator (as addressed previously) for global CVD risk, including atherosclerotic CVD and heart failure.[18,104,146,147] The CKM guidance recommends SGLT2 inhibitors for patients with CKD to reduce CVD

Table 3. Risk Mitigation for Side Effects of SGLT2 Inhibitors and GLP1 Receptor Agonists[140]

Adverse Events	Potential Mitigating Strategies
SGLT2 Inhibitors	
Genital mycotic infections	• Daily hygiene to keep genital area clean and dry
Volume depletion	• Diuretic dose reduction in patients at risk for hypovolemia • Hold SGLT2 inhibitors during acute illness (nausea, vomiting, diarrhea) • Implement sick day protocol
DKA	• Educate patients on early recognition • "STOP DKA" protocol (stop SGLT2 inhibitor, test for ketones, maintain fluid and carbohydrate intake, insulin)
Amputation	• Encourage foot self-examinations • Examinations by health care professionals at each visit
Hypoglycemia	• Dose adjustment of insulin and insulin secretagogues with maintenance of at least low-dose insulin to avoid DKA
GLP1 Receptor Agonists	
Nausea/vomiting/diarrhea	• Patient education on tolerability and symptom recognition • Start at lowest dose and titrate slowly
Hypoglycemia	• Adjustment of background antihyperglycemic agents, as appropriate

Abbreviations: DKA, diabetic ketoacidosis; GLP1, glucagon-like peptide 1; SGLT2, sodium/glucose cotransporter 2.

events as well as kidney disease events. Broadening CKD education and implementation efforts across nephrology, primary care, endocrinology, and cardiology could encourage use of these and other guideline-directed medical therapies. Therefore, efforts to increase implementation and reduce barriers, including high medication costs, are clearly needed.

Mineralocorticoid Receptor Antagonists

In the 2024 KDIGO CKD guideline, a key recommendation and practice points from the "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease"[111] was highlighted, which was also discussed in detail in the "KDOQI Commentary on the KDIGO 2022 Update Clinical Practice Guideline for Diabetes Management in CKD."[120]

Recommendation 3.8.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, and eGFR >25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

Practice Point 3.8.1: Nonsteroidal MRA are most appropriate for adults with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Practice Point 3.8.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.8.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

Practice Point 3.8.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 3.8.5: A steroidal MRA may be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among people with a low GFR.

Commentary and Clinical Utility

Finerenone is the only nonsteroidal mineralocorticoid receptor antagonist currently approved for use in the United States. The kidney and cardiovascular benefits of finerenone were established through 2 major clinical trials: the Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) trial and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial.[3,8] FIDELIO-DKD and FIGARO-DKD found relative risk reductions of 18% and 13% for their primary kidney and cardiovascular composite outcomes, respectively. The reduction in CVD risk was primarily attributable to a reduction in heart failure hospitalizations. It is important to note that the kidney and cardiovascular risk reductions with finerenone occurred with background ACEI or ARB inhibitor treatment. The FIDELITY meta-analysis of both trials together reported similar benefits of finerenone on reducing kidney and CVD risks across a range of baseline eGFR from 25 to >60 mL/min/1.73 m^2 and UACR levels of 30 to ≥300 mg/g and irrespective of atherosclerotic CVD.[148,149] The KDOQI Work Group agrees with the KDIGO guidelines, the ADA-KDIGO consensus report, and the ADA "Standards of Care in Diabetes—2024," which recommend that finerenone be added as additional risk-based therapy in persons with type 2 diabetes and UACR > 30 mg/g while on a SGLT2 inhibitor and maximally tolerated dose of an ACEI or ARB or an ACEI

or ARB alone. The KDOQI Work Group prioritizes SGLT2 inhibitors over finerenone therapy as the next step after baseline ACEI/ARB therapy because SGLT2 inhibitors have a larger effect on reducing both kidney and cardiovascular outcomes.[135,148] However, finerenone should be considered if a person does not tolerate a SGLT2 inhibitor or remains with albuminuria despite being on an SGLT2 inhibitor.[77,121] Although finerenone may have a lower risk for hyperkalemia compared with steroidal mineralocorticoid receptor antagonists, potassium monitoring remains essential to prevent and manage hyperkalemia. Serum potassium should be monitored prior to drug initiation and periodically during treatment.[111,121]

Implementation and Challenges

Finerenone was approved for the treatment of CKD in patients with type 2 diabetes in the United States in July 2021 and in the European Union in February 2022. Although it is too early to assess the use rates of finerenone, prescriptions for conventional mineralocorticoid receptor antagonists were given to 9.8% of patients with diabetes and CKD during 2019-2020 in the CURE-CKD Registry.[126] These data suggest that finerenone prescribing will likely need attention for implementation strategies while additional studies to understand its use alone and in combination with SLGT2i as well as potential barriers including high medications costs are warranted. The US patent for finerenone does not expire until 2029, thus it will be some time before lower-cost generic products will be available.

Glucagon-like Peptide-1 Receptor Agonists

In the 2024 KDIGO CKD guideline, a key recommendation and practice point from the "KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease"[111] was highlighted which was also discussed in detail in the "KDOQI Commentary on the 2020 KDIGO Clinical Practice Guideline for Diabetes Management in CKD."[113]

Recommendation 3.9.1: In adults with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

Practice Point 3.9.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Commentary

Assessing available clinical trial evidence, the KDOQI Work Group agrees with the KDIGO statement on the use of GLP1 receptor agonists in persons with type 2 diabetes and CKD. In addition to the established atherosclerotic CVD benefits of agents with GLP1 receptor agonists, evidence continues to build substantiating their benefits on CKD in patients with or without diabetes.[150-154] Additionally, a glycemic control trial in participants with type 2 diabetes and moderate-to-severe CKD (participants with eGFR as low as 15 mL/min/1.73 m^2) reported a significantly slower rate of eGFR decline with dulaglutide treatment compared with insulin glargine.[155] Importantly, this trial also established glycemic lowering efficacy and safety in patients with moderate-to-severe CKD.

Recent pooled analyses with participants from liraglutide and semaglutide CVOTs further substantiate albuminuria lowering and slower eGFR decline compared with placebo, with benefit observed in those with baseline eGFR < 60 mL/min/1.73 m^2.[156,157] Since publication of the 2024 KDIGO CKD guideline, the Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial has provided the first primary kidney disease outcomes data with a GLP1 receptor agonist in participants with type 2 diabetes and CKD. This trial of subcutaneous semaglutide, 1 mg weekly, versus placebo was stopped early for clear positive efficacy. The primary composite kidney outcome (≥50% eGFR decline, eGFR <15 mL/min/1.73 m^2, dialysis or transplant, death due to kidney disease or CVD) was reduced by 24% with a hazard ratio of 0.76 (95% CI, 0.66-0.88) with consistent findings across multiple subgroups defined by demography, eGFR, UACR, metabolic parameters, and CVD status.[158,159] Notably, the rate of eGFR decline measured as slope was significantly slowed along with reduced risks of major atherosclerotic CVD events and all-cause mortality.

The SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial, a phase 3 CVOT of semaglutide (2.4 mg weekly) versus placebo in overweight or obese persons with preexisting CVD and without diabetes, reported a positive result on its primary outcome of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death) with a relative risk reduction of 20%.[160] The secondary "nephropathy" outcome (macroalbuminuria onset, ≥50% eGFR decline, kidney failure, or death due to kidney disease) was reduced by 22% with a hazard ratio of 0.78 (95% CI, 0.63-0.96). Because only 21% had an eGFR < 60 mL/min/1.73 m^2 or UACR ≥ 30 mg/g at baseline in SELECT, these data support that CKD may be prevented by semaglutide in overweight or obese persons without diabetes.[161,162] CVOT evidence is also emerging for benefits of a dual GLP1/glucose-dependent insulinotropic (GIP) receptor agonist, tirzepatide, on kidney and CVD outcomes based on reductions in albuminuria and rate of eGFR decline in persons with type 2 diabetes as well as those who are overweight or obese.[163] Therefore, it is reasonable to anticipate updated guideline recommendations for use of GLP1 receptor agonists in CKD, perhaps extending beyond diabetes.

Clinical Utility

The metabolic effects of GLP1 receptor agonists are well-established, with preserved glycemic-lowering in advanced CKD, reduction of BP by approximately 3-4 mm Hg, and mean weight reduction of approximately 3 kg.[155,164-166] Kidney protective effects of GLP1 receptor agonists are not fully explained by reductions in glycemia, BP, and weight. In a mediation analysis of completed CVOTs with liraglutide and semaglutide, lower glycemia, BP, and weight only modestly mediated (10%-25%) development of A3 or severe albuminuria, doubling of Scr and decline in eGFR to <45 mL/min/1.73 m^2, or progression to kidney failure, suggesting direct protective effects of GLP1 receptor agonists in the kidney.[167]

Gastrointestinal side effects are the most common dose-limiting side effect of GLP1 receptor agonists and tirzepatide. Starting at the lowest dose and titrating judiciously to achieve tolerability is prudent. Counseling patients on the importance of eating smaller portions, eating slowly, and stopping eating once full, and avoiding high-fat and/or spicy foods can help minimize gastrointestinal intolerance.[111,121,168] Given the preserved glycemic-lowering effect of GLP1 receptor agonists even in advanced CKD, adjusting background insulin secretagogue or insulin therapies may be warranted to prevent hypoglycemia.

Implementation and Challenges

Similar to underutilization of ACEI/ARB and SGLT2 inhibitor, 6.8% of patients with diabetes and CKD were prescribed a GLP1 receptor agonist in the CURE-CKD Registry during the years 2019-2020.[126] Persistent use of a GLP1 receptor agonist for at least 90 days was 6.3%. In patients with commercial health insurance as recently as 2020, GLP1 receptor agonist initiation was reported in 17% of patients with diabetes and CKD.[144] Data from the VA health system showed similar slower uptake of GLP1 receptor agonists.[169] Based on the FLOW trial results, CKD per se in patients with type 2 diabetes may become an additional indication. CKM guidance from the AHA recommends GLP1 receptor agonists for patients with type 2 diabetes or obesity to reduce atherosclerotic CVD risk, weight, and glycemia.[18,147] Extending education and implementation efforts across nephrology, primary care, endocrinology, cardiology, and pharmacy could encourage the use of GLP1 receptor agonists and other guideline-directed medical therapies for patients with CKM conditions. Liraglutide should be the first GLP1 receptor agonist with kidney and cardiovascular benefits to obtain generic status, possibly in 2024.[144] Similar to SGLT2 inhibitors and finerenone, efforts to increase implementation and reduce barriers, including high medication costs, are clearly needed.

Metabolic Acidosis

Practice Point 3.10.1: In people with CKD, consider use of pharmacological treatment with or without dietary intervention to prevent development of acidosis with potential clinical implications (e.g., bicarbonate <18 mmol/l in adults).

Practice Point 3.10.2: Monitor treatment for metabolic acidosis to ensure it does not result in serum bicarbonate concentrations exceeding the upper limit of normal and does not adversely affect BP control, serum potassium, or fluid status.

Commentary and Clinical Utility

Despite several observational studies demonstrating potential harmful effects of metabolic acidosis on kidney disease progression and mortality, clinical trials examining the treatment of metabolic acidosis in CKD have been limited. Also, a large clinical trial examining the benefits of veverimer (to correct metabolic acidosis) did not demonstrate a decline in a composite CKD progression outcome, which was attributed to the lack of difference in serum bicarbonate between the treatment and control groups.[170] Thus, the KDOQI Work Group agrees that until additional trials become available, acidosis in adults should only be treated with pharmacologic agents when bicarbonate < 18 mmol/l or if there is a clear indication to do so. A reasonable goal would be to increase bicarbonate levels toward but not greater than the normal range with sodium bicarbonate or other agents. Pediatric clinicians may choose to treat milder acidosis more aggressively to help optimize growth and bone health.

We also support prevention and treatment of metabolic acidosis through increased dietary intake of fruits and vegetables. The "KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update" reinforces this with their statement 6.1.1.[114] In adults with CKD 1-4, we suggest reducing net endogenous acid production through increased dietary intake of fruits and vegetables (2C) to reduce the rate of decline of residual kidney function.[114]

Implementation and Challenges

It is important to acknowledge that the Mediterranean diet, which emphasizes fruits and vegetables, is costly and is not easily accessible for many patients with CKD who live in underresourced communities. It is encouraging that the Fruits and Veggies for Kidney Health randomized parallel trial has supported the feasibility of identifying low-income community-dwelling Black individuals with increased ACR as well as implementing and sustaining a fruit and vegetable diet with or without cooking instructions over 6 months. Participants who received fruits, vegetables, and cooking instructions saw a 31% decrease in their 6-month ACR, as their intake of these foods increased.[171]

Hyperkalemia in CKD

3.11.1. **Awareness of factors impacting on potassium measurement**

Practice Point 3.11.1.1: Be aware of the variability of potassium laboratory measurements as well as factors and mechanisms that may influence potassium measurement including diurnal and seasonal variation, plasma versus serum samples, and the actions of medications.

3.11.2. **Potassium exchange agents**

Practice Point 3.11.2.1: Be aware of local availability or formulary restrictions with regards to the pharmacologic management of nonemergent hyperkalemia.

3.11.3. **Timing to recheck potassium after identifying moderate and severe hyperkalemia in adults.**

[No recommendations and practice points]

3.11.4. **Managing hyperkalemia**

[No recommendations and practice points]

3.11.5. **Dietary considerations**

Practice Point 3.11.5.1: Implement an individualized approach in people with CKD G3–G5 and emergent hyperkalemia that includes dietary and pharmacologic interventions and takes into consideration associated comorbidities and quality of life (QoL). Assessment and education through a renal dietitian or an accredited nutrition provider is advised.

Practice Point 3.11.5.2: Provide advice to limit the intake of foods rich in bioavailable potassium (e.g., processed foods) for people with CKD G3–G5 who have a history of hyperkalemia or as a prevention strategy during disease periods in which hyperkalemia risk may be a concern.

Commentary and Clinical Utility

The Work Group agrees and strongly advocates dietary counseling as an adjunct to the management of hyperkalemia. When discussing diet, however, we advocate for considering cultural preferences and sensitivities around diet. In addition, for adolescents and young adults as well as for patients in underresourced communities, we would advocate for dietary options that are both affordable and easily accessible.

The Work Group also supports a thorough investigation into alternative medication products that patients may be taking during the medication reconciliation process. Several herbal products or supplements can raise potassium levels, including potassium supplements and salt substitutes, alfalfa, dandelion, horsetail, Lily of the Valley, milkweed, and nettle. Prescribed medications such as direct renin inhibitors, verapamil, and mannitol require increased potassium monitoring in patients with CKD.[172] Strategies to achieve and maintain normal potassium levels include dietary adjustments, adjusting diuretic doses, and/or utilizing SGLT2 inhibitors as well as address hypertension, hypervolemia, and/or the risk of CKD progression and cardiovascular events to avoid the negative consequences of a prescribing cascade (adding on another medication simply to treat an adverse effect). The KDOQI Work Group suggests considering the use of new potassium binders rather than stopping RAS inhibitors or mineralocorticoid receptor antagonists in the setting of hyperkalemia and considering sodium polystyrene sulfonate as an alternative (only for short-term use) in underresourced settings after attempts to obtain new potassium binders have been made.

The KDOQI Work Group agrees that utilization of potassium binding agents could help some patients with high potassium levels maintain ACEI/ARB and/or mineralocorticoid receptor antagonist use. Patiromer and sodium zirconium cyclosilicate are advantageous in that they do not need to be administered 3 times daily like sodium polystyrene sulfonate, which increases the likelihood of medication adherence and lessens the possibility of a binding-related interaction with the plethora of other medications that persons with CKD typically take. The 12-week randomized, double-blind, placebo-controlled AMBER trial showed that patients randomized to spironolactone and patiromer or placebo demonstrated that 86% of patiromer versus 66% of placebo-treated participants were able to remain on spironolactone at week 12.[173] The DIAMOND trial (randomized, double-blind, placebo controlled) evaluated the efficacy of continued patiromer to maintain target doses of RAS inhibitors compared with patiromer withdrawal in persons with heart failure, hyperkalemia, and RAS inhibitor use; 48.3% had stage G3 or G4 CKD before randomization.[174] Although the results showed that continued patiromer treatment versus placebo reduced the risk of hyperkalemic events and increased the likelihood of maintaining at least 50% of target mineralocorticoid receptor antagonist dose, only 44% completed 18 weeks of therapy, and only 17% completed 54 weeks of therapy. The in-between group difference in serum potassium at study end was only −0.10 mmol/L, with greater difference (−0.19 mmol/L) in the subgroup with eGFR < 45 mL/min/1.73 m^2.

Implementation and Challenges

Cultural preferences, lack of access to healthy foods, and more access to processed foods with bioavailable potassium increases the challenges of achieving and maintaining normokalemia. A helpful framework for considering barriers and facilitators of healthy eating in persons with CKD was published in 2020.[175] In preliminary results from the "Five Plus Nuts and Beans for Kidney" study of Black adults with CKD, a group who were coached on buying fresh food with potassium when compared with a group who were not coached showed that initial food subsidies and consistent coaching increased fruit and vegetable consumption and dietary potassium while reducing UACR in persons with values ≥300 mg/g at baseline. Coaching was found to have more impact than food subsidies, and no person

developed hyperkalemia (potassium > 5.5 mEq/L).[176] Cost and availability of potassium resins may limit their utility in patients in underresourced settings with inadequate insurance [Practice Point 3.11.2], and low adherence may limit their overall utility. The high cost of new medications coupled with insurance companies, pharmacy benefit managers, and health systems that limit access through formulary restrictions and utilization management (prior authorization, step therapy, quantity or dose limits) make it difficult for many patients to afford these medications. Although pharmaceutical companies have patient financial assistance programs, finding these programs, obtaining patient data, and filling out paperwork require a time commitment nearly impossible for the practitioner, health system, or patient to manage.

Anemia

The "KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease" is anticipated to be updated and published in 2024, which will be reviewed by the KDOQI Work Group.

CKD-Mineral Bone Disorder

Recommendations and practice points pertained to CKD–mineral bone disorder (CKD-MBD) management have been discussed in the "KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)."[177]

Hyperuricemia

Recommendation 3.14.1: We recommend people with CKD and symptomatic hyperuricemia should be offered uric acid-lowering intervention *(1C)*.

Practice Point 3.14.1: Consider initiating uric acid-lowering therapy for people with CKD after their first episode of gout (particularly where there is no avoidable precipitant or serum uric acid concentration is >9 mg/dl [535 μmol/l]).

Practice Point 3.14.2: Prescribe xanthine oxidase inhibitors in preference to uricosuric agents in people with CKD and symptomatic hyperuricemia.

Practice Point 3.14.3: For symptomatic treatment of acute gout in CKD, low-dose colchicine or intra-articular/oral glucocorticoids are preferable to nonsteroidal anti-inflammatory drugs (NSAIDs).

Dietary approaches

Practice Point 3.14.4: Nonpharmacological interventions which may help prevent gout include limiting alcohol, meats, and high-fructose corn syrup intake.

Recommendation 3.14.2: We suggest not using agents to lower serum uric acid in people with CKD and asymptomatic hyperuricemia to delay CKD progression *(2D)*.

Commentary and Clinical Utility

Because patients with CKD have been traditionally excluded from studies involving gout treatment, gout management has been based on clinical trial data of populations without CKD.[178] The STOP-Gout randomized controlled trial was an exception in that it deliberately enrolled persons with eGFR 30-59 mL/min/1.73 m^2 (39% of total) and compared the efficacy of allopurinol and febuxostat to prevent gout flares. The results showed that allopurinol was noninferior to febuxostat in patients with stage 3 CKD. The American College of Rheumatology recommends initiating uric acid–lowering therapy (ULT) in patients with evidence of destructive gout or in patients with >2 gout attacks a year[179] and conditionally recommends the initiation of ULT in patients with CKD stages G3-5 due to risk of progressive joint disease based on an observational study.[180]

Given that data are lacking in people with CKD, we recommend individualized treatments and shared decision making. Medication and lifestyle adjustments should be considered after the first gout episode in adults with CKD.

Controversy exists regarding optimal allopurinol dosing in patients with CKD. The most concerning adverse effect is allopurinol hypersensitivity syndrome (AHS), which usually occurs within 6-8 weeks after initiation and has been associated with CKD, initial allopurinol dose, and the presence of the HLA*B5801 allele.[181,182] A retrospective study showed a strong association between the starting (not maintenance) dose of allopurinol and AHS.[183] Their results indicated that an initial dose of 1.5 mg per unit of eGFR would reduce the risk of AHS. Given the available oral allopurinol dose strengths (100, 300 mg), the practical application of this research is starting with allopurinol at 100 mg for eGFR 45-60 mL/min and at 50 mg (half of a 100 mg tablet) per day in patients with eGFR < 45 mL/min. If the patient tolerates that dose over the first 6 weeks, the dose can be increased to 200 mg or 100 mg, respectively, and further titrated up as needed based on target uric acid levels of ≤6 mg/dL and patient tolerance. Restricting the maintenance dose of allopurinol to lower "adjusted for kidney function" initial doses in persons with CKD results in failure to reach target uric acid concentrations.[184]

We agree that low-dose colchicine or intra-articular/oral glucocorticoids are preferable to nonsteroidal anti-inflammatory drugs for symptomatic treatment of acute gout flare, but "low-dose" was not defined in the guideline. The FDA approved dosing for colchicine is 1.2 mg followed by 0.6 mg an hour later for acute flares. Colchicine is partially eliminated by the kidneys. A single-dose pharmacokinetic study with 0.6 mg showed that colchicine kidney clearance was decreased by 44% and 65% in persons with eGFR 30-59 and 15-29 mL/min/1.73 m^2, respectively. Total body clearance in persons with CKD stage G3 and G4 was about half of that in those without CKD. However, the maximum concentration after the dose in each eGFR group was similar to that found in individuals with normal kidney function.[185] This suggests that the usual dose (1.2 mg) should be given for the first dose, but the second dose may not be

needed. Multiple dose pharmacokinetic and safety studies across CKD stages are needed to support chronic dosing for preventing gout flares. Colchicine is also metabolized by the P450 enzyme CYP3A4 and potent CYP3A4 inhibitors (eg, macrolide antibiotics, diltiazem, verapamil, itraconazole, ketoconazole, cyclosporine, and ritonavir/nirmatrelvir [Paxlovid]), which may result in increased risk of colchicine exposure and should not be used concomitantly in patients with or without CKD.[186] We advocate for comanagement of acute and recurrent symptomatic gout with rheumatology.

Implementation and Challenges

Diets advocated for patients with gout are plant-based and require access to additional dietary resources for patients living in food deserts, having lower income, and/or having inadequate access to transportation.

Checking HLA*B5801 seems appropriate in high-risk populations (Han Chinese, Korean, Thai, and African descent) with CKD who are being considered for initiation of allopurinol therapy to avoid severe cutaneous adverse reactions, as up to 9% of these populations may have this allele.[181] However, this pharmacogenomic test may not be easily available or financially feasible for many high-risk populations in the United States who are being assessed for treatment with these agents. On a positive note, the availability of genomics and pharmacogenomic programs within health systems is increasing.

In addition, online Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines are continuously being updated.[187] Several CPIC guidelines include tools to aid in implementation of these programs for medication-related decision making (eg, Clinical Implementation Workflow for Electronic Health Records).[181] However, insurers and health systems must recognize the benefit of genomic/pharmacogenomic testing in high-risk patients and the risk of potential lawsuits given CPIC guidelines. They must also develop a business plan, incorporate clinical decision support within the EHR, and educate clinicians (typically pharmacists) on how to counsel patients at increased risk of adverse medication effects as part of personalized comprehensive medication management. Appropriate ULT dosing in CKD is still controversial and requires close monitoring for adverse drug effects in individual patients. Education to combat practitioner misconceptions that some ULTs have adverse kidney effects, and thus require conservative dosing (eg, allopurinol, febuxostat), may result in ineffective uric acid lowering and symptom control. The consensus statement from the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) notes that future trials of ULTs need to include patients with CKD across the eGFR spectrum with subgroup analyses for each CKD stage.[188] In addition, longer-term studies are needed with ULTs that are used for flare prophylaxis in persons with CKD.

Cardiovascular Disease (CVD) and Additional Specific Interventions to Modify Risk

3.15.1 Lipid management

The benefits of lowering low-density lipoprotein cholesterol using statin-based therapies on the risk of atherosclerotic CVD is well-established in people with and without CKD. There are clear recommendations on when to initiate such therapies set out in the "KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease."[189] The Work Group concurs with all the recommendations in this guideline. In particular, we draw attention to the following recommendations.

Recommendation 3.15.1.1: In adults aged ≥50 years with eGFR <60 ml/min per 1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination *(1A)*.

Recommendation 3.15.1.2: In adults aged ≥50 years with CKD and eGFR ≥60 ml/min per 1.73 m^2 (GFR categories G1–G2), we recommend treatment with a statin *(1B)*.

Recommendation 3.15.1.3: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following *(2A)*:

- known coronary disease (myocardial infarction or coronary revascularization),
- diabetes mellitus,
- prior ischemic stroke, or
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

Practice Point 3.15.1.1: Estimate 10-year cardiovascular risk using a validated risk tool.

Practice Point 3.15.1.2: In people with CKD, choose statin-based regimens to maximize the absolute reduction in low-density lipoprotein (LDL) cholesterol to achieve the largest treatment benefits.

Practice Point 3.15.1.3: In adults with CKD aged 18–49, a lower (i.e., <10%) estimated 10-year incidence of coronary death or non-fatal myocardial infarction may also be appropriate thresholds for initiation of statin-based therapy.

Practice Point 3.15.1.4: Consider prescribing proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors to people with CKD who have an indication for their use.

Dietary approaches

Practice Point 3.15.1.5: Consider a plant-based "Mediterranean-style" diet in addition to lipid-modifying therapy to reduce cardiovascular risk.

Commentary and Clinical Utility

The risk of CVD exceeds the risk of progression to kidney failure for the majority of people with CKD;[190,191] therefore, careful attention to the diagnosis and treatment of CVD is needed to improve quality of life and improve survival of persons with CKD. This chapter

provides a comprehensive overview of atherosclerotic CVD and its treatments, including treatment of lipid disorders. Dyslipidemia is common in CKD, and routine clinical practice includes measurement of lipid profiles. Treatment initiation of therapies such as statins is based on the risk and benefits of the therapy, independent of the lipid levels. Unchanged from previous guidelines in 2013,[192] the KDIGO guidelines recommend initiation of statin treatment in adults with CKD not treated with dialysis or kidney transplant. Clinical trial data support general safety of statins in persons with CKD. However, data from trials also suggest that the benefits of statins decrease as eGFR declines[193-195] and that maximal safe doses may differ in those receiving dialysis; therefore, the guidelines specifically focus on those with mild to moderate CKD.

Implementation and Challenges

Chapter 3.14 focuses on atherosclerotic CVD and does not comment on heart failure, which has comparable risk to (or even exceeds) atherosclerotic CVD.[196,197] While the guidance on use of statins is sound, implementation of recommendations 3.14.11, 3.14.12, and 3.14.1.3 may have challenges. Per the guidelines, the "at risk" groups who may benefit from a statin include those with CKD aged 18-49 years with an estimated 10-year incidence of coronary death or nonfatal myocardial infarction of >10% or people with CKD over the age of 50 years. However, these risk scores generally have not performed well in those with CKD, particularly those with advanced CKD.[198,199] Newer risk prediction scores, including the PREVENT score,[104,146] may help improve cardiovascular risk stratification, allowing clinicians and patients to carefully weigh risks versus benefits of additional therapies across the age span.

Additionally, other novel therapies for treatment of dyslipidemia include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. A pooled analysis of 4,629 individuals from 8 phase 3 clinical trials examined the effect of alirocumab (a monoclonal antibody to PCSK9) versus placebo in participants with versus without CKD. This study found that alirocumab substantially lowered low-density lipoprotein levels regardless of the presence of CKD.[200] However, these studies did not include individuals with advanced stages of CKD. Although these results are encouraging, more data on CVD outcomes in persons with a broad range of kidney function are needed. Until then, there continues to be uncertainty in lipid management in patients with advanced CKD and those treated with dialysis.

3.15.2 **Use of antiplatelet therapy**

Recommendation 3.15.2.1: We recommend oral low-dose aspirin for prevention of recurrent ischemic cardiovascular disease events (i.e., secondary prevention) in people with CKD and established ischemic cardiovascular disease *(1C)*.

Practice Point 3.15.2.1: Consider other antiplatelet therapy (e.g., $P2Y_{12}$ inhibitors) when there is aspirin intolerance.

Commentary and Clinical Utility

Antiplatelet therapy is commonly used for primary and secondary treatment of atherosclerotic CVD in general populations.[201] Aspirin is low cost and widely available, facilitating implementation. KDIGO has a class C recommendation for oral low-dose aspirin in the secondary prevention of recurrent ischemic cardiovascular events in persons with CKD based on available clinical trial data. A Cochrane collaboration meta-analysis found that treatment with antiplatelet therapy may reduce the relative risk of myocardial infarction by 12% (risk ratio, 0.88; 95% CI, 0.79-0.99).[202] There were no studies analyzed that examined primary prevention, and antiplatelet medication use was associated with an expected relative increase in major bleeding (risk ratio, 1.35; 95% CI, 1.10-1.65) and minor bleeding (risk ratio, 1.55; 95% CI, 1.27-1.90) in persons with CKD. Based on this meta-analysis, there is uncertain effect on risk of stroke and death.[202] Therefore, the evidence to use aspirin for secondary prevention of recurrent atherosclerotic disease events is moderate at best in persons with CKD, given potential harm with only modest reduction in risk of myocardial infarction.

Implementation and Challenges

There is a paucity of literature on primary prevention strategies (including antiplatelet agents) for CVD in persons with CKD. Careful studies are needed to understand the best approaches for primary prevention, carefully balancing possible harm with benefits. Patients with CKD may have greater risk of adverse events such as bleeding (as seen in the Cochrane meta-analysis for secondary prevention). Further, a patient-centered approach is needed to account for patient preferences, pill burden, and quality of life.

3.15.3 **Invasive versus intensive medical therapy for coronary artery disease**

Recommendation 3.15.3.1: We suggest that in stable stress-test confirmed ischemic heart disease, an initial conservative approach using intensive medical therapy is an appropriate alternative to an initial invasive strategy *(2D)*.

Practice Point 3.15.3.1: Initial management with an invasive strategy may still be preferable for people with CKD with acute or unstable coronary disease, unacceptable levels of angina (e.g., patient dissatisfaction), left ventricular systolic dysfunction attributable to ischemia, or left main disease.

Commentary and Clinical Utility

The guidelines highlight the recent clinical trials comparing invasive versus intensive medical therapy for coronary heart disease in patients with CKD and recommend that an initial conservative approach using medical therapy is appropriate for stable stress test–confirmed ischemic heart disease. The ISCHEMIA-CKD trial randomized 777 persons with advanced CKD and moderate or severe ischemia on stress testing to be treated with an initial invasive strategy (coronary angiography and revascularization added to medical therapy) versus medical therapy alone, with angiography reserved for those in whom medical therapy had failed.[203] The trial found no difference between the invasive versus conservative strategy; additionally, the invasive strategy may have had higher incidence of death and initiation of dialysis.[203]

However, KDIGO and the AHA/ACC[204] emphasize that an invasive strategy may be preferable for persons with CKD and acute or unstable angina, unacceptable levels of angina (limiting quality of life), or left ventricular systolic dysfunction attributable to ischemia or left main disease, which is a reasonable approach, carefully weighing the risks versus benefits of invasive therapies.

Implementation and Challenges

A conservative approach seems very reasonable as recommended by the KDIGO guidelines. However, efforts should be made to ensure that high-risk patients (those with acute or unstable angina) are not withheld invasive strategies for treatment of coronary heart disease that could significantly improve morbidity and mortality.[205] Decisions around eligibility for invasive procedures or surgery may be particularly challenging in patients with advanced stages of CKD and kidney failure, who may not have typical presentations of acute coronary symptoms.[206]

Additionally, procedures may be held due to fear of complications, especially in patients with advanced CKD. When angiography is clinically needed, the risk of contrast-induced AKI should not be a reason to forego cardiac catheterization in most patients with CKD.[204] When possible, attempts to minimize the risk of contrast nephropathy should be made through the avoidance of nephrotoxic agents, use of adequate hydration before and after the administration of iodinated contrast-agent, and minimization of the volume of contrast media. There is no benefit of bicarbonate or N-acetyl-L-cysteine over normal saline for prevention of AKI.[207]

3.16 CKD and atrial fibrillation

Practice Point 3.16.1: Follow established strategies for the diagnosis and management of atrial fibrillation.

Recommendation 3.16.1: We recommend use of non-vitamin K antagonist oral anticoagulants (NOACs) in preference to vitamin K antagonists (e.g., warfarin) for thromboprophylaxis in atrial fibrillation in people with CKD G1–G4 *(1C)*.

Practice Point 3.16.2: NOAC dose adjustment for GFR is required, with caution needed at CKD G4–G5.

Practice Point 3.16.3: Duration of NOAC discontinuation before elective procedures needs to consider procedural bleeding risk, NOAC prescribed, and level of GFR.

Commentary and Clinical Utility

Atrial fibrillation is the most common sustained arrythmia in adults worldwide, with particularly high incidence and prevalence in persons with CKD. Risk of atrial fibrillation increases with more advanced CKD stages.[208] The KDIGO guideline highlights the high burden of atrial fibrillation in CKD and provides a summary of anticoagulation options including use of novel oral anticoagulants (NOACs), more commonly known as direct oral anticoagulants (DOACs). Based on subgroup analyses of large clinical trials of DOACs, the KDIGO guidelines recommend use of DOACs (vs warfarin) for thromboprophylaxis in persons with G1 to G4 CKD and atrial fibrillation. Although the evidence supports the use of DOACs in mild to moderate CKD, there is more uncertainty on the safety and efficacy of DOACs (and anticoagulation overall) in persons with more advanced stages of CKD (eg, G4 and G5). For example, the recent RENAL-AF trial randomized patients receiving maintenance hemodialysis to apixaban versus warfarin. Although the study was not powered to draw conclusions for safety or efficacy, the pharmacokinetic data suggested that kidney function had a relatively small contribution to the pharmacokinetics of apixaban.[209] Another recent trial, the AXADIA trial, also randomized patients receiving maintenance hemodialysis to a vitamin K antagonist versus apixaban and found no difference in efficacy or safety (although the trial was likely underpowered).[210,211]

Implementation and Challenges

The identification of atrial fibrillation remains challenging in persons with CKD. Using symptoms, electrocardiograms, or Holter monitors underestimates the true burden of atrial fibrillation in this population[212] because the clinical presentation may differ and/or symptoms may overlap with those frequently attributable to CKD. In the future, wearable devices may improve the detection of atrial fibrillation in high-risk patients with CKD.

The CHA_2DS_2-VASc risk score (Congestive heart failure, Hypertension, Age, Diabetes, and Stroke/transient ischemic attack, Vascular disease, Age, Sex category) is widely used to estimate risk of thromboembolism in persons with atrial fibrillation, but the performance of the risk score in persons with CKD is not well-studied. As the KDIGO guideline points out, about 95% of people with eGFR < 60 mL/min/1.73 m^2 have a CHA_2DS_2-VASc score of ≥ 2. These data suggest that the risk score does not discriminate thromboembolism risk among persons with CKD.

Although presence of CKD heightens risk of thromboembolism, the risks and benefits of anticoagulation remain uncertain (irrespective of the type of anticoagulation used) in persons with advanced CKD. To date, most studies with a "no treatment" group have been observational and/or inconclusive. Lack of good evidence leads to clinical uncertainty on whether to anticoagulate persons with advanced CKD and atrial fibrillation. Future trials are needed to test this important question.

Medication Management and Drug Stewardship in CKD

The role of a clinical pharmacist, a vital stakeholder in optimizing medication management, is not well-delineated as a member of the multidisciplinary care team. In the United States (and in a number of other countries) clinical pharmacists frequently work directly with persons with diabetes and hypertension (and as an extension—CKD) to provide "comprehensive medication management" utilizing a team-based care approach. Comprehensive medication management is defined as the standard of care that ensures each patient's medications (ie, prescription, nonprescription, alternative, traditional, vitamins, or nutritional supplements) are individually assessed to determine that each medication is appropriate for the patient, effective for the medical condition, safe given the individual's comorbidities and concurrent medications, and able to be taken by the patient as intended.[213] Pharmacists focused on chronic condition management (including diabetes and hypertension) have demonstrated improvement in medication adherence, diabetes parameters, BP, and patient and provider satisfaction, and have reduced hospitalization and contributed to health-related cost savings.[127-132] The KDOQI Work Group recommends that future guidelines incorporate the key role of the clinical pharmacist in the multidisciplinary care of those with CKD.

Medication Choices and Monitoring for Safety

Practice Point 4.1.1: People with CKD may be more susceptible to the nephrotoxic effects of medications. When prescribing such medications to people with CKD, always consider the benefits versus potential harms.

Practice Point 4.1.2: Monitor eGFR, electrolytes, and therapeutic medication levels, when indicated, in people with CKD receiving medications with narrow therapeutic windows, potential adverse effects, or nephrotoxicity, both in outpatient practice and in hospital settings.

Practice Point 4.1.3: Review and limit the use of over-the-counter medicines and dietary or herbal remedies that may be harmful for people with CKD.

Medications and pregnancy

Practice Point 4.1.4: When prescribing medications to people with CKD who are of child-bearing potential, always review teratogenicity potential and provide regular reproductive and contraceptive counselling in accordance with the values and preferences of the person with CKD.

Commentary and Clinical Utility

The KDOQI Work Group agrees that patients with CKD may be more susceptible to the nephrotoxic effects of medications. Impairment of medication metabolism in setting of CKD also increases the risk of adverse effects from prescribing errors that may lead to under- or overdosing of important medications or interactions related to polypharmacy. Prescribing in this population should carefully consider risks, potential benefits, and potential harms, which are later addressed in the KDIGO guideline. For example, when prescribing medications such as antidepressants, muscle relaxants, medications used for nerve pain, and opioid pain medications, each must be considered in terms of side effects in the context of CKD and dosed appropriately because increased adverse effects have been described in this population.[214]

In addition to monitoring those medications with a narrow therapeutic window, the KDOQI Work Group believes that the inclusion of medications with potential effects on kidney function and electrolytes, including but not limited to SGLT2 inhibitors, RAS inhibitors, and mineralocorticoid receptor antagonists, would be important. Further, clinical and laboratory monitoring should occur at prespecified, planned intervals upon prescribing to minimize the occurrence of adverse events.[9,111]

Though outside the scope of the special population of people with CKD of childbearing potential, we would also highlight other special populations exist, such as individuals on immunosuppressive agents for organ transplant or other clinical conditions, in whom it is important to review potential drug interactions of newly prescribed medications and counsel on such.

Implementation and Challenges

Medications with narrow therapeutic windows may include antiarrhythmic agents, anticonvulsants, chemotherapy, and antibiotics. The narrow therapeutic range of medication benefits versus harms can be further narrowed in patients with declining eGFR in the setting of AKI, CKD progression, or heart failure exacerbation or volume depletion. Educating patients on when to hold medications, such as during acute illnesses, may help reduce adverse effects of medications.

Dose Adjustments by Level of eGFR

Practice Point 4.2.1: Consider GFR when dosing medications cleared by the kidneys.

Practice Point 4.2.2: For most people and clinical settings, validated eGFR equations using SCr are appropriate for drug dosing.

Practice Point 4.2.3: Where more accuracy is required for drug-related decision-making (e.g., dosing due to narrow

therapeutic or toxic range), drug toxicity, or clinical situations where eGFRcr estimates may be unreliable, use of equations that combine both creatinine and cystatin C, or measured GFR may be indicated.

Practice Point 4.2.4: In people with extremes of body weight, eGFR nonindexed for body surface area (BSA) may be indicated, especially for medications with a narrow therapeutic range or requiring a minimum concentration to be effective.

Practice Point 4.2.5: Consider and adapt drug dosing in people where GFR, non-GFR determinants of the filtration markers, or volume of distribution are not in a steady state.

Commentary and Clinical Utility

The KDOQI Work Group agrees with the importance of dosing medications that may be excreted by the kidneys through individual assessment of eGFR. The KDOQI Work Group agrees with the recommendations of FDA, the NKF-ASN Task Force, and the Advancing Kidney Health Through Optimal Medication initiative that GFR adjusted for an individual's body surface area (BSA) in mL/min ($eGFR_{BSAadj}$) should generally be utilized for pharmacologic dosing considerations where variations in body habitus exist. Adjusting eGFR for an individual's BSA may be particularly important in the United States given that overweight status and obesity are common.[215] Adjustment for an individual's BSA can be completed by multiplying the standardized eGFR by the patients BSA/1.73 m^2 or by using the NKF eGFR calculator which allows users to input an individual's height and weight to allow calculation of BSA.[216] It will also allow for comparison in mL/min between eGFR and creatinine clearance,[111,217,218] which is the current method that most pharmacists use to determine drug dosage adjustments.[219]

Implementation and Challenges

Although cystatin C may be helpful to incorporate in eGFR measurements, specifically in situations with increased risk of drug toxicity, cystatin C is currently not readily available in all laboratories for rapid decision making. Given these barriers and challenges, the KDOQI Work Group feels that the most accurate, available, individualized measurement should be utilized for drug dosing while also incorporating individualized assessments of the therapeutic window of the medication.[217,218]

Polypharmacy and Drug Stewardship

Practice Point 4.3.1: Perform thorough medication review periodically and at transitions of care to assess adherence, continued indication, and potential drug interactions because people with CKD often have complex medication regimens and are seen by multiple specialists.

Practice Point 4.3.2: If medications are discontinued during an acute illness, communicate a clear plan of when to restart the discontinued medications to the affected person and healthcare providers, and ensure documentation in the medical record.

Practice Point 4.3.3: Consider planned discontinuation of medications (such as metformin, ACEi, ARBs, and SGLT2i) in the 48–72 hours prior to elective surgery or during the acute management of adverse effects as a precautionary measure to prevent complications. However, note that failure to restart these medications after the event or procedure may lead to unintentional harm (see Practice Point 4.3.2).

4.3.1. **Strategies to promote drug stewardship**

Practice Point 4.3.1.1: Educate and inform people with CKD regarding the expected benefits and possible risks of medications so that they can identify and report adverse events that can be managed.

Practice Point 4.3.1.2: Establish collaborative relationships with other healthcare providers and pharmacists and/or use tools to ensure and improve drug stewardship in people with CKD to enhance management of their complex medication regimens.

Commentary and Clinical Utility

Polypharmacy has been associated with an increased risk of adverse events including decreased adherence and increased emergency department visits, hospitalizations, health care costs, and mortality in the general population. Patients with CKD have been described as taking a median of 8 medications.[220] Patients who take 5 or more medications have been described as having an increased risk of kidney failure, cardiovascular events, and all-cause mortality as compared with those who take fewer. Medication reconciliation for patients with CKD is essential given the risks of polypharmacy. The importance of this occurrence should be highlighted around transitions in location of care (eg, transitioning out of a health care facility including hospital, rehabilitation unit or nursing home) as well as around clinical transitions, such as initiation of dialysis, or a diagnosis of a new disease state that may alter prognosis and therapeutic indices of certain medications. Communication of updated changes in medications should occur with all members of the patient care team, including caretakers and pharmacies.

In addition to medication reconciliation, consideration of deprescribing, defined as a systematic process of identifying and discontinuing drugs in instances where existing or potential harm outweigh existing or potential benefit, should occur. Deprescribing in the older patient population has been associated with decreased mortality, decreased referrals to nursing homes, lower drug costs, and improved health perception, and most importantly it was not associated with increased risks of adverse outcomes.[221] In addition to considerations for deprescribing, each medication should be evaluated for indication, effectiveness, and safety as well as whether the patient can obtain and take the prescribed medication as intended to promote drug safety and adherence. Adjustments to a patient's medications should be followed with a clearly communicated plan for patient follow-up monitoring.[222]

Medication discontinuation is important around certain clinical events, and instructions regarding whether and when the medications should be resumed must be clearly communicated. We agree with highlighting the potential negative consequences of not resuming these medications. In addition to documenting in the medical record, efforts should be made to clearly communicate with all members of the care team.

A thorough discussion of risks, benefits, and possible side effects should occur when prescribing new medications to patients with CKD. A pharmacist should be included in this counseling, if one is available. Specific considerations of time to benefit when prescribing medications, particularly in older patients or those patients who may have a limited life expectancy, should also be taken into account to limit the potential risks and polypharmacy. The risks and benefits of a prescribing cascade in this population should be highlighted, especially in the setting of polypharmacy.[223] We again highlight the need for an individualized approach. Medications may sometimes be started in response to a side effect of another medication, such as the initiation of diuretic therapy in response to edema caused by a calcium channel blocker or gabapentin.[224] Effective alternative agents to the calcium channel blocker or gabapentin may exist and should be considered before prescribing a second medication to treat undesired effects. In some instances, a prescribing cascade may be considered acceptable in which the offending medication has a morbidity or mortality benefit without an alternative option. For example, a potassium-binding resin may be prescribed to treat hyperkalemia from an ACEI or ARB. When prescribing new medications, an evaluation of necessity, a medication reconciliation to determine whether deprescribing of another medication may be indicated first, and a discussion of risks, benefits, and time to benefit should occur with patients.

Implementation and Challenges

Limitations exist in the ability to complete and communicate medication reconciliation, deprescribing, and recommendations for resuming medications that may be held around procedures across care teams. Patients may receive care in various health care systems, and there is no universal shared electronic medical record, which can complicate this communication.

We agree that incorporation of a pharmacist as part of the CKD multidisciplinary team to provide comprehensive medication management can improve patient safety by addressing polypharmacy, deprescribing, and counseling when new medications are prescribed; however, we also recognize that highly trained clinical pharmacists with CKD and cardiometabolic disease expertise may be a limited resource in some areas of the United States. The Advancing Kidney Health Through Optimal Medication Management initiative has created a multidisciplinary curriculum for physicians, nurse practitioners, physician assistants, nurses, and pharmacists to improve their knowledge and skills in optimizing medication management for persons with CKD and CKM syndrome.[225]

Imaging Studies

Practice Point 4.4.1: Consider the indication for imaging studies in accordance with general population indications. Risks and benefits of imaging studies should be determined on an individual basis in the context of their CKD.

4.4.1. Radiocontrast: intra-arterial and intravenous dye studies

Practice Point 4.4.1.1: Assess the risk for AKI in people with CKD receiving intra-arterial contrast for cardiac procedures using validated tools.

Practice Point 4.4.1.2: The intravenous administration of radiocontrast media can be managed in accordance with consensus statements from the radiology societies in people with AKI or GFR <60 ml/min per 1.73 m^2 (CKD G3a–G5) undergoing elective investigation.

4.4.2. Gadolinium-containing contrast media

Practice Point 4.4.2.1: For people with GFR <30 ml/min per 1.73 m^2 (CKD G4–G5) who require gadolinium-containing contrast media, preferentially offer them American Colleague of Radiology group II and III gadolinium-based contrast agents.

Optimal Models of Care

KDIGO CKD guidelines discuss referral to kidney specialty care services to optimize patient outcomes. As noted by others,[226] this is a rather narrow view because it omits the myriad opportunities to optimize kidney and cardiovascular health "upstream" using team-based care within primary care before advanced kidney disease necessitates nephrology referral.

Two recent cluster randomized, pragmatic studies of kidney health interventions within the primary care setting (ICD-Pieces and Kidney CHAMP) examined the impact of electronically augmented primary care clinician decision support combined with either practice facilitator or multidisciplinary primary care support, respectively.[73,74] Although neither study showed an improvement in the primary outcome (1 year hospitalization rate and rate of decline of eGFR over 17 months, respectively), both studies were hampered by enrollment of populations with limited performance gap in some targeted measures (eg, BP control), relatively short follow-up periods, and being conducted in the era before SGLT2 inhibitors and GLP1 receptor agonists. Both studies were also impacted by the restrictions in the delivery of care arising during the COVID-19 era. In addition, both studies enrolled patients with significantly impaired kidney function to start (mean eGFR of stage 3a and 3b, respectively). Thus, the question of utility of early, stand-alone EHR-based primary care decision support interventions to optimize kidney health outcomes remains unsettled.

Several integrated health care systems in the United States, such as the Veterans Health Administration, foster a collaborative care approach between primary and specialty nephrology care where referral may be to address a single question or to request shared care in the delivery of guideline-directed medical therapy. This approach facilitates early access to nephrology support in the management of those with early CKD with the aim of mitigating disease progression upstream and the need for patient care transfer to specialty care. Yet even integrated health systems with collaborative care agreements wrestle with the seemingly universal constraints of limited primary care and nephrology work forces, patient and provider knowledge gaps related to CKD, and limited electronic clinician decision support tools, presenting the challenge of how best to manage complex care across the continuum of CKD within such constraints.

Chapter 5 focuses on the management of people with advanced CKD. However, some of the practice points in the chapter are applicable to clinicians in the primary care setting, such as Practice Point 5.1.1 which includes the use of risk prediction models to optimize the triage of patients at high risk of kidney failure to specialty care for shared or full subsequent care.

Likewise, Practice Point 5.3.3 enjoins clinicians to consider nontraditional modes of delivery of nephrology care such as e-consults and tele-nephrology care, to enable access to specialty care to all who need it. Future iterations of the guideline would benefit from a review of strategies to enhance patient and provider awareness of CKD and to screen for CKD in high-risk populations to optimize the care of people with CKD. In addition, a global broad environmental scan of strategies to improve the implementation of evidence-based guideline recommendations across the full spectrum of CKD and within the context of different health resource environments is needed. Lastly, it has been increasingly recognized that CKD presents as part of a composite of cardiovascular, kidney, and metabolic disorders, and is significantly modified by social determinants of health.[18] Optimal future models of care of CKD therefore need to adopt an even more holistic approach, addressing not only how to deliver patient-centered guideline-directed medical therapies targeting the scope of disturbances characterizing the CKM syndrome, but also how to do so in a way that mitigates care fragmentation across multidisciplinary teams and attends to modifiable social determinants of health.

Referral to Specialist Kidney Care Services

Practice Point 5.1.1. Refer adults with CKD to specialist kidney care services in the following circumstances listed in Figure 5.

Special considerations

Pediatric considerations

Practice Point 5.1.2: Refer children and adolescents to specialist kidney care services in the following circumstances:

- an ACR of 30 mg/g (3 mg/mmol) or a PCR of 200 mg/g (20 mg/mmol) or more, confirmed on a repeat first morning void sample, when well and not during menstruation,
- persistent hematuria,
- any sustained decrease in eGFR,
- hypertension,
- kidney outflow obstruction or anomalies of the kidney and urinary tract,
- known or suspected CKD,
- recurrent urinary tract infection.

Commentary and Clinical Utility

Given the differences in practice patterns and availability of nephrologists, the KDOQI Work Group believes that greater clarity regarding the indication for nephrology referral is desirable because referral based solely on an absolute eGFR threshold is not patient-centered nor cost effective. Such a referral paradigm may result in a missed opportunity for earlier preventive intervention in a high-risk patient yet generate unnecessary demand for specialty care services for a multitude of low-risk patients, overwhelming the health system capacity for specialty care.[227] Thus, we applaud the expanded consideration of criteria for nephrology referral beyond eGFR threshold of 30 mL/min/1.73 m^2, as well as the inclusion of risk of kidney failure as a more patient-centered indicator for referral as illustrated in Figure 5.

Furthermore, although we agree that the use of a risk estimation equation by primary care clinicians may optimize the judiciousness of referrals to kidney specialists, the question remains: How do we incorporate risk prediction equations into clinical workflow to promote their consistent and effective use? Recent reports suggest that the provision of a KFRE alert is insufficient to maximize the utility of the score and that education of patients and providers on the appropriate interpretations of KFRE scores and thresholds to guide clinical care is necessary.[109]

Implementation and Challenges

The KDOQI Work Group recognizes various implementation challenges such as limited assessment of albuminuria in primary care, lack of CKD awareness among patients, and difficulty with interpreting the information provided by the KFRE and other risk equations as barriers to timely referral to nephrology for further care. There are ongoing efforts by NKF, ASN, and other organizations to address these barriers, which have been discussed in detail in previous sections of this document.

Symptoms in CKD

5.2.1. **Prevalence and severity of symptoms**

[No recommendations and practice points]

5.2.2 **Identification and assessment of symptoms**

Practice Point 5.2.2.1: Ask people with progressive CKD about uremic symptoms (e.g., reduced appetite,

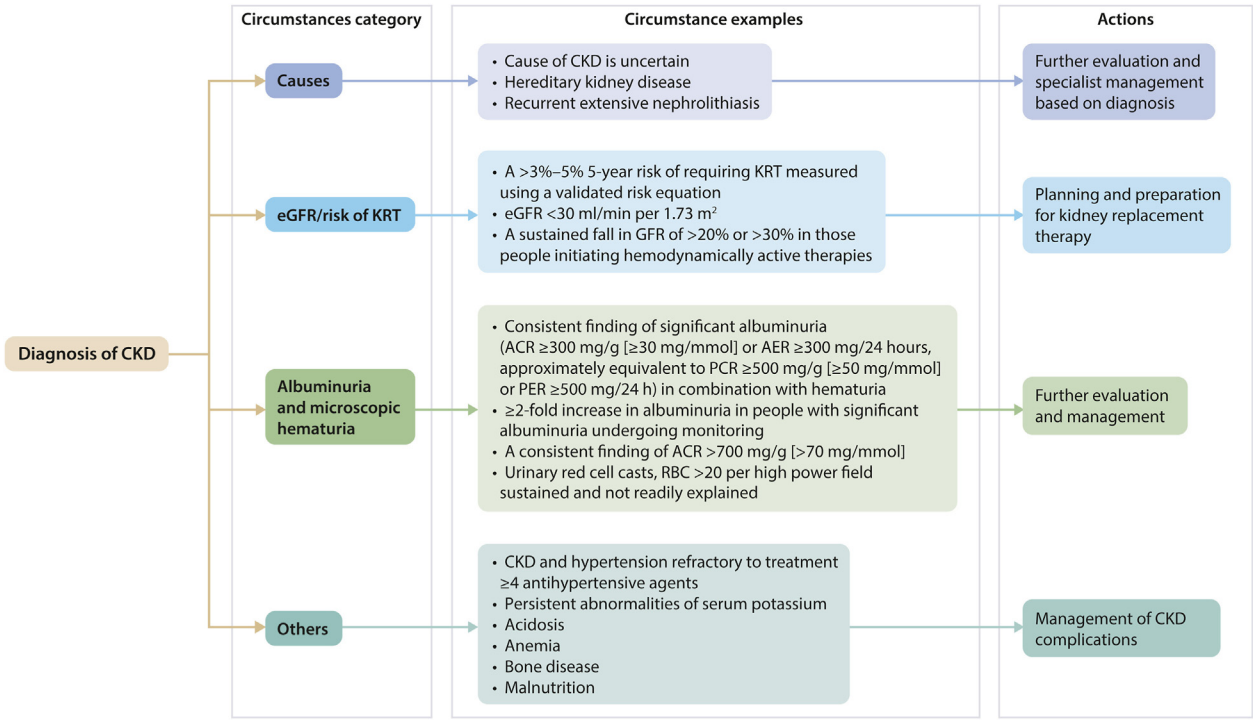

Figure 5. Circumstances for referral to specialist kidney care services and goals of the referral. ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; PCR, protein-creatinine ratio; PER, protein excretion rate; RBC, red blood cells. Image ©2024 KDIGO; reproduced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024 Apr;105(4S):S117-S314[23] with permission of the copyright holder.

nausea, and level of fatigue/lethargy) at each consultation using a standardized validated assessment of uremic symptoms tool.

5.2.3. **Management of common symptoms for people with CKD**

Practice Point 5.2.3.1: Use evidence-informed management strategies to support people to live well with CKD and improve their health-related quality of life.

Practice Point 5.2.3.2: Screen people with CKD G4–G5, aged >65, poor growth (pediatrics), or symptoms such as involuntary weight loss, frailty, or poor appetite twice annually for malnutrition using a validated assessment tool.

Practice Point 5.2.3.3: Enable availability of appropriate medical nutrition therapy for people with signs of malnutrition, ideally under the supervision of renal dietitians or accredited nutrition providers if not available.

Commentary and Clinical Utility

As noted in Practice Point 5.2.2, we agree and applaud the focus on a patient-centered approach to the recognition and management of symptom burden for patients with CKD because it affects quality of life.

Similarly, as discussed in the practice point 5.2.3.2, we agree that an assessment of malnutrition is appropriate in patients > 65 years old with CKD stage G4-5 and poor growth in children with CKD. This assessment, however, should be undertaken by a practitioner who is knowledgeable about the utilization of these validated malnutrition tools—ideally this would be a licensed dietitian.

Team-based Integrated Care

Practice Point 5.3.1: Enable access to a patient-centered multidisciplinary care team consisting of dietary counselling, medication management, education, and counselling about different KRT modalities, transplant options, dialysis access surgery, and ethical, psychological, and social care for people with CKD.

Practice Point 5.3.2: Education programs that also involve care partners where indicated are important to promote informed, activated people with CKD.

Practice Point 5.3.3: Consider the use of telehealth technologies including web-based, mobile applications, virtual visiting, and wearable devices in the delivery of education and care.

Special considerations

Pediatric considerations

5.3.1. Transition from pediatric to adult care

5.3.1.1. Pediatric providers

Practice Point 5.3.1.1.1: Prepare adolescents and their families for transfer to adult-oriented care starting at 11–14 years of age by using

checklists to assess readiness and guide preparation, and by conducting part of each visit without the parent/guardian present.

Practice Point 5.3.1.1.2: Provide a comprehensive written transfer summary, and ideally an oral handover, to the receiving healthcare providers including all relevant medical information as well as information about the young person's cognitive abilities and social support.

Practice Point 5.3.1.1.3: Transfer young people to adult care during times of medical and social stability where possible.

5.3.1.2. Adult providers

Practice Point 5.3.1.2.1: Recognize that young people under 25 years of age with CKD are a unique population at high risk for adverse outcomes at least in part due to physiologic incomplete brain maturation.

Practice Point 5.3.1.2.2: Encourage young people to informally visit the adult care clinic to which they will be transferred before the first appointment.

Practice Point 5.3.1.2.3: Assess young people with CKD more frequently than older people with the same stage of CKD and, with the agreement of the young person, include the caregivers or significant other of the young person in their care, at least in the first 1–3 years following transfer from pediatric care.

Commentary and Clinical Utility

We concur with the lead statement that the optimal model of care should be defined as one that achieves the best outcomes, balancing the benefits for patients, the population, and the community. Such a model for patient care, retaining caring as its central element and applying the ethical principles of medicine to the clinical expertise available, is necessary to promote health care justice.

Multidisciplinary Care Team. The delivery of the proposed health services necessary to meet the full aim of Practice Point 5.3.1 is sufficiently expansive to require practicing within an integrated health care system. Consequently, unless partnered within a comprehensive managed care payment model, the feasibility of enacting this practice point within US nephrology private practices may be limited.

Regarding the discussion on the specific components for CKD models of care, we believe that the hierarchy of proposed elements should begin with the provision of primary care and health system resources to enable appropriate screening for and subspecialty referral of patients with CKD. Inclusion of education programs should follow, targeting primary care clinicians and patients to close extant knowledge gaps and to empower patients to make informed decisions about their kidney health care choices, respectively.[228]

Care Transitions. We agree that the transition of care between pediatric and adult nephrology care is especially challenging and requires both special attention and established protocols from pediatric and adult nephrologists alike. Recognizing that emerging adulthood is a high-risk time period for all young adults, especially for those with chronic illness, is critical for adult providers who care for these patients. Young adults with CKD may also have added cognitive challenges that may also impact their intellectual maturity which in turn may affect their time line for successful transition and integration into the adult health care system.[229] We therefore recommend that within a practice a transition champion(s) partners with a pediatric nephrologist(s) to ensure optimal communication and care for this population. If available, medicine-pediatric trained specialists can bridge the gap during this transition of care.

We also agree that the timing of transfer should occur during a medically and psychosocially stable period in a patient's life. The patient, however, should also be included in the discussion around appropriate timing and planning of transfer of care.[230]

Implementation and Challenges

The implementation of a successful transitions of care program, bringing young patients with CKD from pediatric to adult nephrology, requires significant resources and expertise. Medicine-pediatric specialists are well-suited for bridging this gap but may not be available in most places across the United States. Transition champions, as referenced previously, may not also have the training to shepherd a young adult from pediatric to adult nephrology care. Transition surveys may highlight some self-management skills that are needed prior to transition to adult care, but they have never been shown to predict successful transition. Young adults who are deemed ready to transition require ongoing support throughout their adjustment into adult care, regardless of their transition survey results. Patients and their families should be an integral part of the discussion regarding timing and process of transition, though sometimes this transition may occur too late, at a time in a young adult's life when a parent is not as present.

Educational Materials. Additional educational resources and curriculum are needed for adult nephrologists to assume the care of young adults with CKD because of the growing volume of referrals from pediatric nephrologists.

We agree that if educational materials are written for patients and families, the materials should be explained clearly, preferably set at fifth grade level to optimize understanding. Cultural customization of materials may also enhance patient uptake of information. To maximize the reach of patient education and to address the needs of nonliterate people with CKD, alternatives to print materials for the delivery of educational content should be

considered, such as virtually delivered educational content, inclusion of family members/caregivers in education sessions, and interactive virtual group education sessions for live question and answer opportunities. We also suggest that a supplementary table of developed CKD patient education resources be included for interested readership. The table could point to materials developed by federal agencies and reputable nonprofits.

Technology-based Delivery of Kidney Care. With regard to the use of telemedicine to deliver kidney health services, we would suggest including e-consultation to the methods of asynchronous care, as has been studied in a VA-led effort in CKD virtual care.[228,231]

Implementation and Challenges

Currently, a significant gap exists between the goal of delivering CKD patient education and the reality of its actual delivery. Several US studies have shown significant selection bias in the delivery of CKD patient education and suggest that the consequences of referral biases for patient education are an important driver of disparities in the delivery of kidney health services, such as home dialysis. Tele-technology has been proposed to extend the reach of CKD education, especially in health systems with limited resources, and by using standardized content it can reduce disparities in the receipt of comprehensive CKD education. Tele-education has been shown to be feasible and to improve patient outcomes in several non-CKD conditions. For patients with CKD, tele-education has been found to be noninferior to face-to-face education in increasing patient home dialysis selection rates and confidence in dialysis decision making.[232]

A growing role for telemedicine to augment dissemination of CKD education to both clinicians as well as to patients is foreseen. Ongoing studies comparing the efficacy of telemedicine with face-to-face standardized CKD education on patient and health services outcomes should provide more guidance.[233]

Timing the Initiation of Dialysis

Practice Point 5.4.1: Initiate dialysis based on a composite assessment of person's symptoms, signs, QoL, preferences, level of GFR, and laboratory abnormalities.

Practice Point 5.4.2: Initiate dialysis if the presence of one or more of the following situations is evident (original guideline Table 41). This often but not invariably occurs in the GFR range between 5 and 10 ml/min 1.73 m^2.

Practice Point 5.4.3: Consider planning for preemptive kidney transplantation and/or dialysis access in adults when the GFR is <15-20 ml/min per 1.73 m^2 or risk of KRT is >40% over 2 years.

Commentary and Clinical Utility

The evidence available to inform recommendations about the timing of initiation of dialysis remains limited, and this results in practice points very similar to those included in the 2012 guidelines.[234] Importantly, the KDOQI Work Group agrees with the foundational and patient-centered new declaration that initiation of dialysis should be informed by multiple dimensions of a patient's health and livelihood. Similar to the 2012 commentary, we again assert that symptoms should be assessed regularly and considered during the shared decision-making process of determining the time to initiate dialysis.

The KDIGO guidelines continue to expound on considering initiation of dialysis as "early" or "late" defined by eGFR and highlights its impact on mortality. At this point, a consideration may be to abandon the labels of early or late, which impart judgment that the decision point missed opportunities and recognize that 1 factor (eg, eGFR) is insufficient to determine the desired accepted time point, or time window, of starting dialysis. Further, if no difference in outcomes based on the timing of initiation has been identified, then the reason for characterizing initiation as early or late comes into question. Without clear evidence of impact on outcomes, then it suggests the objective is to determine whether there is a problem with health care access (eg, "late") or perhaps medical procedure overuse (eg, "early"). While important questions, these may be considered apart from defining recommendations about when to initiate dialysis for individual patients and making subsequent judgments to decide if the initiation timing was appropriate.

The final practice point in this section is revised from the prior guidelines to introduce considering dialysis access in addition to pre-emptive transplantation planning. It also introduces the consideration of kidney failure risk prognosis as a prompt for planning. The KDOQI Work Group agrees with the introduction of both components. In addition to the time necessary for successful access planning, the Work Group acknowledges the personalized approach and promotes the KDOQI 2019 Vascular Access guideline recommendation of implementation of vascular access as a key component of a patient's ESKD Life-Plan.[102] Adoption of the recommendations about KFRE implementation in clinical practice (discussed earlier) would further help develop a vascular access plan for initiation of kidney replacement therapy. Preliminary research provides insight into the use of the KFRE along with eGFR to inform decisions about vascular access timing. Small single-center cohort studies align with the suggestion of a 2-year risk of >40%, while others show that the combination of eGFR < 20 mL/min/1.73 m^2 and risk ≥ 20% have a strong association with the combination of dialysis initiation and use of a vascular access and a lower likelihood of not ultimately progressing to kidney failure with an unused preemptive vascular access.[235,236] The guidelines suggest that the majority of physicians will be comfortable in calculating the risk of kidney failure and discussing the risk with patients and caregivers. We agree with this statement, although implementation of the KFRE, for example, as a tool within the EHR remains variable across health systems

and has been discussed previously.[109] Additional rigorous research is needed to advance the understanding of how to best implement the KFRE into dialysis access, but it is a promising tool given the uncertainty related to predicting the trajectories of CKD progression.

Special considerations

Pediatric considerations

Practice Point 5.4.4: In children, in addition to the adult indications for dialysis, poor growth refractory to optimized nutrition, growth hormone, and medical management is an indication for initiating KRT.

Practice Point 5.4.5: Pursue living or deceased donor preemptive kidney transplantation as the treatment of choice for children in whom there is evidence of progressive and irreversible CKD. The eGFR at which preemptive transplantation should be undertaken will depend on multiple factors including the age and size of the child and the rate of progression of kidney failure but will usually be between 5-15 ml/min per 1.73 m^2.

Commentary

The KDOQI Work Group agrees with the additional practice points specific to children when considering preparation and dialysis initiation, with an emphasis on growth and development. The evidence available in children to inform an eGFR threshold or window for initiation is weaker than that in adult populations and more complex, limited by various biases. As with adults, the optimal approach is collaborative decision making individualized to the health and social context of the patient, not limited by specific quantitative measurements.

Structure and Process of Supportive Care and Comprehensive Conservative Management

Practice Point 5.5.1: Inform people with CKD about the options for dialysis and comprehensive conservative care.

Practice Point 5.5.2: Support comprehensive conservative management as an option for people who choose not to pursue KRT.

Practice Point 5.5.3: Provide access to resources that enable the delivery of advance care planning for people with a recognized need for end-of-life care, including those people undergoing conservative kidney care.

Commentary and Clinical Utility

The KDOQI Work Group agrees with retaining in this updated guideline the practice points about supportive care and comprehensive conservative management. Implementation of effective treatment options education and counseling remains a challenge because many patients have low knowledge of their options.[228,237] However, emerging evidence suggests that structured delivery of education employing kidney-specific decision aids results in both informed patients and lower levels of decisional conflict about their treatment choice.[238,239] Future guidelines may consider the growing body of evidence regarding kidney disease education implementation, inclusive of conservative care management, to advance both practice points and recommendations.

In the past decade, there has been a continued dialogue to define, assess, and monitor delivery of kidney supportive care to all patients living with kidney disease, and specifically conservative kidney management as treatment for advanced kidney disease. This was addressed in the recent publication of a comprehensive consensus document from the International Society of Nephrology.[240] The guidelines, similar to the consensus document, recognize the heterogeneity in health care practice settings worldwide, including expertise and availability of resources including personnel, built environments, community culture, and institutional or state support. The Work Group agrees with the basic framework presented in the guidelines but aspires to return to more specific expectations within the practice points to deliver the highest quality care available to patients with kidney disease, such as symptom management, psychological care, and bereavement support both for patients and families.

Conclusion

As we enter an exciting phase for the management of patients with CKD, the updated KDIGO CKD 2024 guidelines provide a comprehensive framework for several critical questions (addressing both diagnosis and management issues) faced by health care providers, policymakers, and patients. The KDIGO 2024 CKD guideline update also includes several recommendations proposed in the previous KDIGO guidelines that focused on management of hypertension and diabetes in persons with CKD and are in concordance with recommendations issued by other organizations (such as ADA) along with expanding this to the broader population. Such a concerted approach would help facilitate both adoption of these recommendations by nephrologists and dissemination of these recommendations to primary care providers who manage a significant proportion of patients with CKD. Several key research recommendations proposed in the guideline document would also help researchers to prioritize the areas of high yield and importance while assisting funding agencies to prioritize topics for funding.

Article Information

Authors' Full Names and Academic Degrees: Sankar D. Navaneethan, MD, MS, MPH, Nisha Bansal, MD, Kerri L. Cavanaugh, MD, MHS, Alexander Chang, MD, MS, Susan Crowley, MD, MBA, Cynthia Delgado, MD, Michelle M. Estrella, MD, MHS, Cybele Ghossein, MD, T. Alp Ikizler, MD, Holly Koncicki, MD, MS, Wendy St. Peter, PharmD, Katherine R. Tuttle, MD, and Jeffrey William, MD.

Authors' Affiliations: Section of Nephrology, Department of Medicine, Selzman Institute for Kidney Health and Institute of Clinical and Translational Research, Baylor College of Medicine

(SDN), and Section of Nephrology, Michael E. DeBakey Veterans Affairs Medical Center (SDN), Houston, Texas; Cardiovascular Health Research Unit, Department of Medicine (NB), and Institute of Translational Health Sciences, Kidney Research Institute, and Nephrology Division (KRT), School of Medicine, University of Washington, Seattle, and Providence Medical Research Center, Providence Inland Northwest Health, Spokane (KRT), Washington; Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, Tennessee (KLC, TAI); Department of Population Health Sciences, Geisinger, Danville, Pennsylvania (AC); Section of Nephrology, Department of Medicine, School of Medicine, Yale University, New Haven (SC), and Kidney Medicine Section, Medical Services, VA Connecticut Healthcare System, West Haven (SC), Connecticut; Nephrology Section, San Francisco Veterans Affairs Health Care System (CD, MME), and Division of Nephrology, University of California–San Francisco (CD, MME), San Francisco, California; Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (CG); Division of Nephrology, Mount Sinai Health System, New York, New York (HK); College of Pharmacy, University of Minnesota, Minneapolis, Minnesota (WS); andDivision of Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (JW).

Address for Correspondence: Sankar D. Navaneethan, MD, MS, MPH, Baylor College of Medicine, Nephrology, Room 100D37, Houston, TX 77030. Email: sankar.navaneethan@bcm.edu or Jeffrey William, MD, Beth Israel Deaconess Medical Center, 171 Pilgrim Rd, Boston, MA 02215. Email: jhwillia@bidmc.harvard.edu

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