KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

CONFIDENTIAL: DO NOT DISTRIBUTE

PUBLIC REVIEW DRAFT

JULY 2023

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with their values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Practice points are consensus-based statements representing the expert judgment of the Work Group and are not graded. They are issued when a clinical question did not have a systematic review performed, to help readers implement the guidance from graded recommendation (e.g., frequency of monitoring, provision of standard care (such as regular clinic visits), referral to specialist care, etc.), or for issuing "good practice statements" when the alternative is considered to be absurd. Users should consider the practice point as expert guidance and use it as they see fit to inform the care of patients. Although these statements are developed based on a different methodology, they should not be seen as "less important" or a "downgrade" from graded recommendations.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

Green, low risk (if no other marker of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. GFR; glomerular filtration rate

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
ACR	mg/g	0.113	mg/mmol
Calcium	mg/dl	0.2495	mmol/l
Creatinine	mg/dl	88.4	µmol/l
PCR	mg/dl	0.113	mg/mmol
Phosphate	mg/dl	0.3229	mmol/l
Urate	mg/dl	0.059	mmol/l

Note: Conventional unit x conversion factor = SI unit

EQUIVALENT ALBUMINURIA CATEGORIES IN CKD

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

*Relative to young adult level
ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease

ABBREVIATIONS AND ACRONYMS

ACEi	angiotensin-converting enzyme inhibitor(s)
ACR	albumin-to-creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AER	albumin excretion rate
AIDS	acquired immune deficiency syndrome
AKD	acute kidney disease
AKI	acute kidney injury
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
BSA	Body surface area
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKiD	Chronic Kidney Disease in Children
CKD-MBD	chronic kidney disease-mineral and bone disorder
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CrCl	creatinine clearance
CT	computed tomography
CVD	cardiovascular disease
DALY	disability-adjusted life year
eGFR	estimated glomerular filtration rate
eGFRcr	creatinine-based estimated glomerular filtration rate
eGFRcr-cys	creatinine and cystatin C-based estimated glomerular filtration rate
eGFRcys	cystatin C-based estimated glomerular filtration rate
EKFC	European Kidney Function Consortium
EMA	European Medicines Agency
ERT	Evidence Review Team
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GLP-1 RA	glucagon-like peptide receptor agonists
GN	glomerulonephritis
HBV	hepatitis B virus
HCV	hepatitis V virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	Health-related quality of life
IgG	immunoglobulin G
IQR	interquartile range
i.v.	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KFRE	Kidney Failure Risk Equation
KRT	kidney replacement therapy
LDL	low-density lipoprotein
LMIC	low- and-middle-income countries
MACE	major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
mGFR	measured glomerular filtration rate
mTOR	mammalian target of rapamycin
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research

NOAC	non-vitamin K antagonist oral anticoagulants
NSAIDS	nonsteroidal anti-inflammatory drugs
OR	odds ratio
OTC	over-the-counter
PCR	protein-to-creatinine ratio
PCSK-9	proprotein convertase subtilisin/kexin type-9
POCT	point-of-care testing
PROM	patient-reported outcome
QoL	quality of life
RAS(i)	renin-angiotensin system (inhibitor)
RAAS(i)	renin-angiotensin-aldosterone system (inhibitor)
RBC	red blood cell
RCT	randomized controlled trial
RR	relative risk
SCr	serum creatinine
SBP	systolic blood pressure
SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
T2D	Tye 2 diabetes
UK	United Kingdom
US	United States
USRDS	United States Renal Data System
WHO	World Health Organization

NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches conducted from July 2022 through February 2023. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare providers using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

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PATIENT FOREWORD

The identification of chronic kidney disease (CKD) begins a long journey for any patient that will have a direct impact on their lifestyle and future health outcomes. These guidelines identify the suitability of medical interventions that can improve or delay the seriousness of CKD and possible kidney failure.

In a complicated world of health provision having a set of evidential recommendations and practice points provide kidney service providers with the targets for a quality CKD service for people with kidney disease. However, if the start point for many people is ignorance of what a kidney actually does, then without a holistic approach to patient care, much of the potential effectiveness of medical interventions can be diluted because of patient circumstances and psychological challenges.

Acceptance of the seriousness of CKD can take a lot longer for a person to process, to the possible detriment of medical intervention and may well lead to issues over adherence.

A controlled, managed CKD decline is so beneficial to patients who have so many social issues to contend with, be it diet, tiredness, liquid control, pill overload, and a deep dive into the very mechanics of a how we eat and drink to survive and excrete excesses.

In an ever-increasingly busy world of medical care, as patients we believe the best approach is for any physician to aim to achieve a partnership of knowledge with the patient regarding their CKD care. This will build patient confidence and self-awareness, with the aim that any patient who sadly arrives at possible dialysis is in the right state of mind, which is critical for a considered approach to the next stage of a patient's journey.

Guy Hill

INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

This 2023 update of the *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* (CKD)[1] is an evidence-based guideline that provides recommendations and practice points for clinical management activities.

The past 10 years have provided new hope for improved treatment of CKD. A greater understanding of healthy lifestyle and lifestyle modifications together with new medications and technologies furnish improved options for treatment and monitoring of CKD. People with CKD, healthcare providers, and health systems are eager to implement these advances in the most effective and evidence-based manner. This requires integration of new therapies with lifestyle management and existing medications using approaches that engage patients and optimize application of health resources. The goal of this guideline is to provide such guidance.

As Co-Chairs, we would like to recognize the outstanding efforts of the Work Group, the Evidence Review Team (ERT), and KDIGO staff. The Work Group was diverse, multinational, multidisciplinary, experienced, thoughtful, and dedicated. Notably, the Work Group included 2 members who have CKD who contributed actively as peers to keep the guideline relevant and patient-centered. We are indebted to each and every individual who contributed to this process. We hope that the guidance provided here will help improve the care of people with CKD worldwide.

The KDIGO 2012 CKD guideline built on the United States (US)-based Kidney Disease Outcomes Quality Initiative (KDOQI) 2002 Guideline on Definition, Classification, and Evaluation of CKD,[2] accepted by the international community in 2005. It reinforced the definition of CKD incorporating persistent reduction in GFR and markers of kidney damage and modified the staging and classification system to include elements that had begun to be appreciated by the clinical community.[3] Specifically, the 2012 guideline introduced the concept of a "CGA" classification of CKD based on cause (C), level of kidney function determined by glomerular filtration rate (G), and degree of albuminuria (A). The CGA classification laid a foundation upon which management, treatment, research, and risk assessment of CKD have since been based.

The definition, staging and classification of CKD proposed by the KDIGO 2012 CKD guideline has been widely accepted and implemented across the world. Research has since highlighted that specific categories of CKD, characterized by level of glomerular filtration rate (GFR) and albuminuria independently, portend greater relative risk for adverse outcomes.[4-7] These include, but are not limited to, CKD progression, cardiovascular disease, mortality (all-cause and cardiovascular), kidney failure, and acute kidney injury (AKI). The development of risk-prediction tools has refined monitoring and referral to specialist nephrology and has aided

in the estimation of prognosis.[6, 8-10] While there remains ongoing discussion about application of the same thresholds to define disease in older adults,[11] it is still clear that even in older populations risk of adverse outcomes increases with higher CKD stages.

This guideline is not intended to be a textbook and recommendations on prevention and screening for CKD, although important topics, are not addressed in depth but are briefly discussed below in the context of the global burden of CKD and in Chapter 1. For a more detailed discussion of these issues, we refer readers to existing textbooks and reviews.[12-14] Prevention and screening for CKD should be conducted mostly by healthcare providers in primary care and in other specialties, such as endocrinology and cardiology, rather than by nephrologists. We strongly support efforts aimed at the early detection and treatment of CKD among people at high risk for CKD, including those with hypertension, diabetes, and cardiovascular disease. Screening efforts in these and other populations should include assessments of GFR (estimated or in certain situations measured) and albuminuria (see Section 1.2).

The intended starting point for this update of the KDIGO 2012 CKD guideline is an established diagnosis of CKD, though there are some practice points to clarify evaluation of CKD and the ascertainment of chronicity. The care of people with CKD is multifaceted and complex. Several critical aspects of this comprehensive care, such as blood pressure (BP), diabetes, and lipid management, have been addressed in other KDIGO guidelines. These topics were not reviewed for the current guideline but recommendations have been incorporated where relevant and we refer readers to those specific KDIGO guidelines and their updates.[15-19]

Several exciting developments have been introduced into clinical practice since the KDIGO 2012 CKD guideline was published. These include refinement of evaluation of GFR, population and individual risk prediction, and novel treatments which have all positively influenced the prognosis for people with CKD. The Work Group has aimed to generate a guideline that is both rigorously devoted to new and existing evidence, and that is clinically useful. The group made specific graded recommendations when supported by high-quality evidence. Practice points are made when either the evidence is insufficient or randomized controlled trials would be impractical/unethical, but clinical guidance was thought to be important and warranted. In some situations, recommendations could be made for some groups of people but not others.

In an iterative process with an ERT, the Work Group, and KDIGO leadership, a series of systematic review questions were selected and refined such that they were both clinically pressing and likely to have a sufficient evidence base to make defensible graded recommendations. Specifically, we focused predominantly on questions that have been

addressed using randomized controlled trials (RCTs) that evaluated clinically relevant outcomes.

Definition and classification of CKD

Defining CKD

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.[1]

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

Table 1. Criteria for chronic kidney disease (CKD) (either of the following present for >3 months).
AER, albumin excretion rate; GFR, glomerular filtration rate

Classifying CKD

CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.[1] These 3 components of the classification system are each critical in the assessment of people with CKD and help enable determination of severity and risk. Listed below are reference tables describing each component. Note that while the definition of CKD includes many different markers of kidney damage and is not confined to decreased GFR and ACR >30 mg/g [>3 mg/mmol], the classification system is based on the 2 dimensions of GFR and degree of albuminuria. This nuance is often missed by healthcare providers and students.

It is well established that patient advocates with CKD and healthcare providers prefer the more clinically useful and generally understood assessment of GFR resulting from the use of GFR estimating equations compared to serum creatinine (SCr) alone. Globally, although still not universally available in all countries, SCr is measured routinely and the approach to assessment of GFR is therefore to **use SCr and an estimating equation for initial assessment of GFR**. The approach to evaluation of GFR using initial and supportive tests is described in greater detail in Chapter 1.

Causes

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, medications, neoplasia (including amyloidosis)	Diffuse, focal, or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, medications, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction, interstitial nephritis
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

Table 2. Classification of chronic kidney disease (CKD) based on presence or absence of genetic and systemic disease and location within the kidney of pathologic-anatomic findings. Genetic diseases are not considered separately because some diseases in each category are not recognized as having genetic determinants. *Note that there are many different ways in which to classify CKD. This method of separating systemic diseases and primary kidney diseases is one proposed by the Work Group to aid in the conceptual approach. ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis

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

Table 3. Glomerular filtration rate (GFR) categories in chronic kidney disease (CKD). *Relative to young adult level. In the absence of evidence of kidney damage, neither G1 nor G2 fulfill the criteria for CKD.

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

Table 4. Albuminuria categories in chronic kidney disease (CKD). *Relative to young adult level. †Including nephrotic syndrome (albumin excretion usually >2200 mg/24hours [ACR >2200 mg/g; >220 mg/mmol]). AER, albumin excretion rate, ACR, albumin-to-creatinine ratio

The global burden of CKD

The Global Burden of Disease, Injuries and Risk Factors Study (GBD) pulls together data on premature death and disability from more than 350 diseases and injuries in 204 countries, by age and sex, from 1990 to the present.[20] Disease "burden" is the impact of a health problem as measured by financial cost, mortality, morbidity, or other indicators and can be measured by combining 2 indicators to describe the disability-adjusted life years (DALYs); the number of years of life lost to disease and the number of years lived with disability due to disease.

Globally, in 2017, systematic analysis from the all-age GBD project found 697.5 million (95% uncertainty interval [UI] 649.2–752.0) cases of all-stage CKD, for a global prevalence of 9.1% (8.5–9.8).[21] By 2021, a joint statement from the American Society of Nephrology, European Renal Association and International Society of Nephrology indicated that more than 850 million people suffer from some form of kidney disease, roughly double the number of people who live with diabetes (422 million) and 20 times more than the prevalence of cancer worldwide (42 million) or people living with acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) (36.7 million).

In 2017, CKD was estimated to account for 35.8 million (95% UI 33.7−38.0) DALYs and 1.2 million people died from CKD. Most of the burden of CKD was concentrated in the 3 lowest quintiles of Socio-Demographic Index (SDI). In 2019 CKD was responsible for 41.5 million (95% UI 38.3-45.0) DALYs and 1.43 million people died from CKD.[20] Age-standardized DALY rates were highest in central and Andean Latin America, at 1348.1 (1203.6–1521.6) and 836.3 (704.2–981.6) per 100,000, respectively (global rate was 514.9 [474.9–558.9]). In 2017, CKD in diabetes represented a third of all DALYs and there were 1.4 million (95% UI 1.2–1.6) cardiovascular disease-related deaths in people with CKD, 25.3 million (22.2 to 28.9) cardiovascular disease DALYs were attributable to impaired kidney function. Overall, CKD and its effect on cardiovascular disease resulted in 2.6 million (95% uncertainty interval 2.4–2.8) deaths in 2017 and CKD has risen from 19th to 11th in rank among leading causes of death between 1990-2019 due to ageing and an increasing burden of risk factors for CKD (including diabetes and hypertension) that, together, contribute to more than half the deaths from CKD.

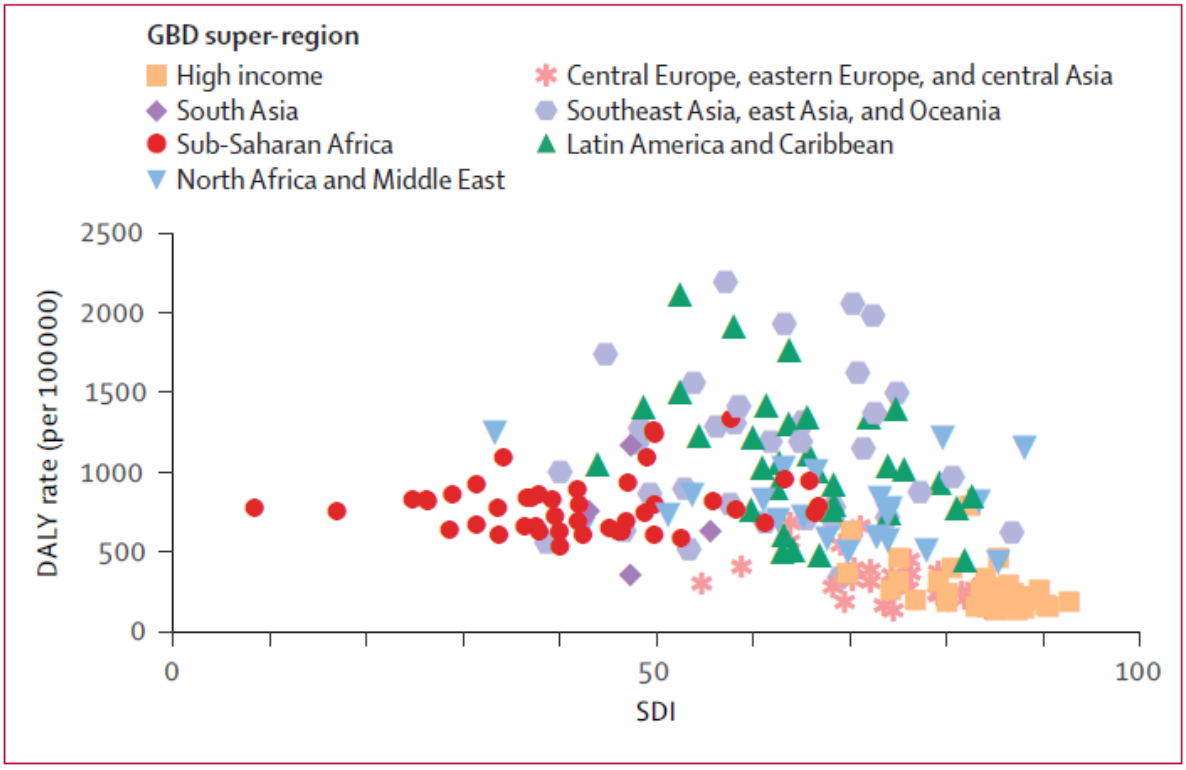

Figure 1. Age-standardized DALY rates for each location by Socio-Demographic Index, both sexes combined, 2019. Reprinted with permission from reference 23[20]

Screening and prevention

Despite the increasing recognition of the true burden of CKD, there remains controversy and lack of consensus as to the utility of population screening for CKD[22] or targeted screening programs,[14] due to the complexity of the underlying sociopolitical and resource environment. Public health policy has a role to play in identifying and addressing risk factors to prevent CKD, to identify CKD early, and to delay its progression and associated adverse outcomes. Education of both health personnel and the populations at risk, implementation of early kidney disease detection programs, and of evidence-based treatment of CKD and its associated conditions, such as BP and diabetes are all essential components of a strategy to address this burden. A systematic review suggested that screening for CKD is cost effective in people with diabetes and hypertension, the 2 most common causes of CKD worldwide.[12] However, clinical trials have not been conducted to determine whether or not an intervention to detect, risk-stratify, and treat CKD would improve the health outcomes for the targeted population. Nevertheless, cost-effective analysis of population-wide screening for CKD incorporating evidence-based treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i) recently concluded that screening adults for albuminuria to identify CKD could be cost-effective in the US.[23]

This evidence aligns with the KDIGO Controversies Conference on Early Detection and Intervention in CKD which concluded that early identification of CKD in people at-risk, who are usually asymptomatic, would likely be beneficial in the community and primary care settings if the programs are interwoven with risk-stratification and treatment.[13] A community program must be able to provide treatment to the high-risk group of patients with newly detected CKD in order to justify systematic early detection strategies. An additional conclusion was that screening and treatment programs for CKD should be implemented based on risk-stratification to prioritize people, particularly in settings with limited economic resources. Whilst globally people with hypertension, diabetes, or cardiovascular disease are at high risk for CKD, other high-risk people may be identified through genetic risk factors or by varying exposure to environmental pollution, pesticides, water, and nephrotoxic medications including significant analgesic use and herbal medications, depending on geographical region. Frameworks in which to consider specific regional factors have been offered to facilitate discussion about the value and context of screening for CKD.[22]

Currently, kidney disease awareness remains low and worldwide only 6% of the general population and 10% of the high-risk population are aware of their CKD status. Important to note is that patient advocates with CKD strongly argue for earlier CKD screening and diagnosis.[13] They also advocate for CKD detection to be integrated with patient and family education and engagement to improve accessing appropriate health care and knowledge and adherence to recommended lifestyle modification and medications.

Use of a simple algorithm such as that shown below in settings such as primary care, cardiology, and endocrinology could significantly improve the early identification and treatment of CKD.

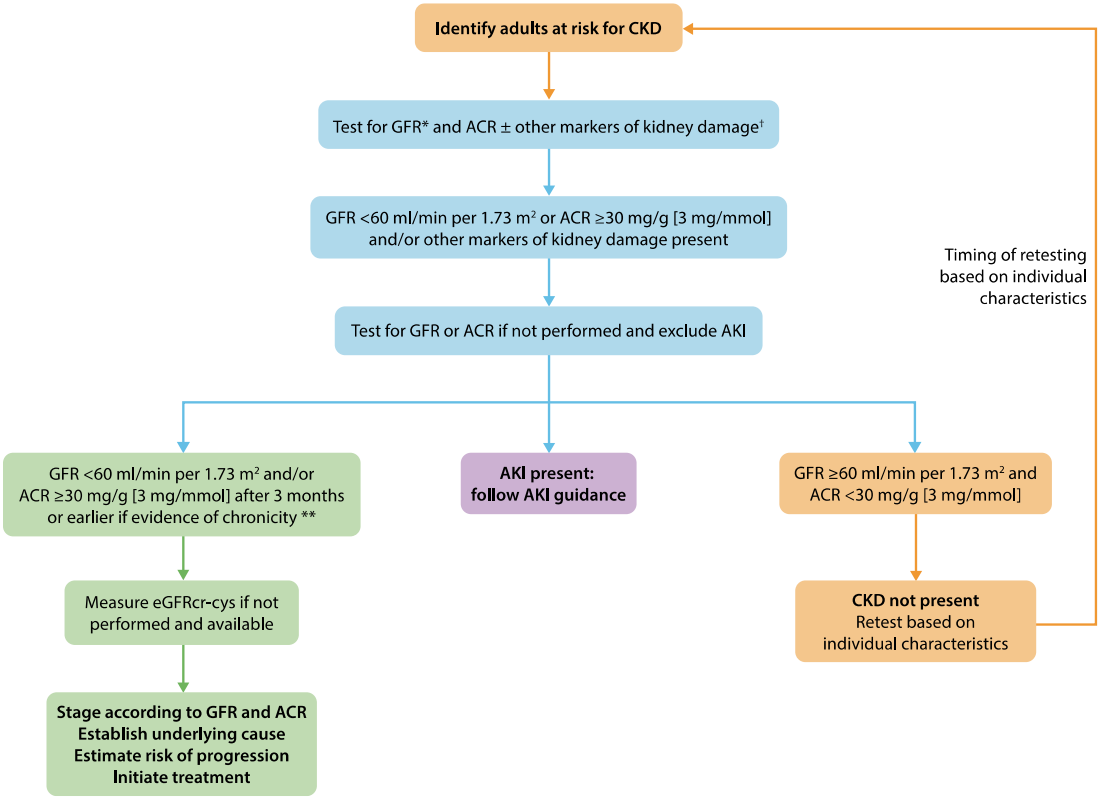

Figure 2. Screening algorithm for diagnosis and staging of chronic kidney disease (CKD). Risk factor conditions include hypertension; diabetes; cardiovascular disease; AKI/hospitalization history; FH kidney disease; obesity; other high-risk comorbidities (e.g., SLE, environmental exposures, nephrotoxic drugs, genetic factors, preeclampsia, low birth weight). *eGFR may be estimated using a creatinine-based estimating equation apart from certain conditions such as patients with large limb amputation, spinal cord injury, neuromuscular disease, severe malnutrition, advanced heart failure, and liver disease where consideration should be given either to use of a combined creatinine-cystatin C estimated GFR, a cystatin C only estimated GFR, or urinary or plasma clearance measurement of GFR. †Markers of kidney damage other than albuminuria may also be used to diagnose CKD, but ACR and GFR should still be evaluated to determine stage and estimate risk of progression. Orange boxes indicate actions in people at risk for CKD and in whom testing should be performed. Blue boxes indicate testing steps. Green boxes indicate identification of CKD and its stages and initiation of treatment. Purple box indicates identification of AKI. Please also see the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*. ACR; albumin creatinine ratio; AKI; acute kidney injury; GFR, glomerular filtration rate; SLE; systemic lupus erythematosus. ** evidence of chronicity

There are no current evidence-based recommendations regarding the frequency of screening in people at risk of CKD. The overall costs of a screening program are largely driven by the frequency of repeat screening, so the timing of repeated testing should be guided by CKD risk. There are risk equations available to estimate the interval risk of developing CKD and this risk-stratification could guide repeat testing intervals.[24]

International considerations

In low- and middle-income regions of the world and in the lower sociodemographic quintiles, there is a large gap between CKD burden and provision of adequate health care. There is limited access to kidney replacement therapy (KRT) combined with rising prevalence of diabetes and hypertension and evidence of substantial sex and gender disparities in access to CKD treatment. These factors highlight the importance of early identification and treatment of risk factors in primary care. However, the majority of the world's population with CKD are in low- and middle-income countries (LMIC) where there are disparities in access to laboratory diagnostic services, kidney biopsy, and imaging services, in availability of appropriately skilled healthcare providers and the availability and affordability of medications. The International Society of Nephrology survey assessing global kidney healthcare resources reported that fewer than 1 in 4 surveyed countries had facilities available for routine measurements of serum creatinine (SCr) or proteinuria.[25]

Importantly, slowing CKD progression at early stages should provide economic benefits and prevent the development of kidney failure and cardiovascular complications. A systematic review of care models in LMIC found that those supporting primary care providers or allied health workers achieved effectiveness in slowing GFR decline, as opposed to interventions centered on specialty care alone.[26] Where there are resource limitations, it is logical to deploy resources where they will be most cost-effective, for example to higher-risk, preventable stages.

Standardization/ accuracy of testing tools including assays/equipment

The KDIGO 2012 CKD guideline was built upon recommendations made to clinical laboratories in the earlier KDOQI 2002 guidance. Clinical laboratories were specifically charged with measuring SCr and serum cystatin C using assays with calibration traceable to the international standard reference materials recommending that, for SCr, there should be minimal bias compared to isotope-dilution mass spectrometry.[1] Recommendations were also made with respect to measurement and reporting of albumin and protein in the urine. Whilst some of the recommendations have become part of routine practice, the effective use of clinical guidelines and therefore, effective patient care, including accurate diagnosis and referral prioritization, clinical research, and public health prioritization. require comparability of laboratory results independent of time, place, and measurement procedure. Key to this is establishing precision and between laboratory agreement with traceability to accepted reference standards wherever available. Therefore, this guidance document includes standards for laboratory tests. The International Consortium for Harmonization of Clinical Laboratory Results (ICHLR) was established to create a pathway for harmonization and aid implementation of clinical guidelines recommending the use of laboratory tests in the diagnosis and management of disease,[27] ensuring that both reference materials and test methodology are harmonized. The ICHLR

aimed to prioritize measurands by medical importance and both coordinate and stimulate development of technical and regulatory processes to achieve harmonization of those measurands.[28] Whilst this has been achieved for SCr, the current status of other key measurands such as cystatin C and urinary albumin is not yet sufficiently clear.

The foundations for this 2023 guideline have been developed over the last 20 years, galvanizing the collaborative work of researchers, healthcare providers, laboratory physicians, patients, and carers. The current updated guideline document reinforces methods for accurate diagnosis of CKD and prediction, incorporates novel treatment strategies and approaches to managing people living with CKD, and identifies further areas for research.

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CKD Guideline Co-Chairs

SPECIAL CONSIDERATIONS

The Work Group recognizes that kidney diseases affect people at different times and with different impacts across the whole lifespan. Thus, enabling a personalized approach, considering age, sex, and gender for diagnosis, risk assessment, and treatment is critical. At the extremes of age - the very young and the very old, diagnostic procedures, treatment aims, treatment modalities, and decision-making differ due to differences in prognosis, treatment options, and prioritization. In young and middle-aged adults, treatment approaches may differ due to specific circumstances, such as pregnancy or menopause. Sex (biological attributes) and gender (sociocultural factors), as well as other important intersectional factors including but not limited to geographical location, socioeconomic position, and race/ethnicity, play important roles in kidney health and disease.

Here we introduce concepts as to why age, sex, and gender should be considered in the context of diagnosis, treatment, and care planning in people with CKD. In addition, the specific guideline chapters incorporate statements where special considerations regarding age, sex, and gender are relevant to clinical practice and understanding.

Considerations in children and adolescents

When the guideline refers to people with CKD, this includes children and adolescents. When there are altered care recommendations and practice points due to the unique needs of children or the lack of data to inform recommendations and practice points, these considerations are discussed within the *Pediatric considerations* sections of the guideline.

The management of children and adolescents with CKD needs special consideration (Figure 3). Children and adults have different etiologies of CKD. Up to 70% of childhood CKD is due to congenital anomalies of the kidneys and urinary tract, which is characterized by slower progression to kidney failure and a higher likelihood of polyuria than the conditions causing CKD in adults. Pediatric CKD has several unique aspects:

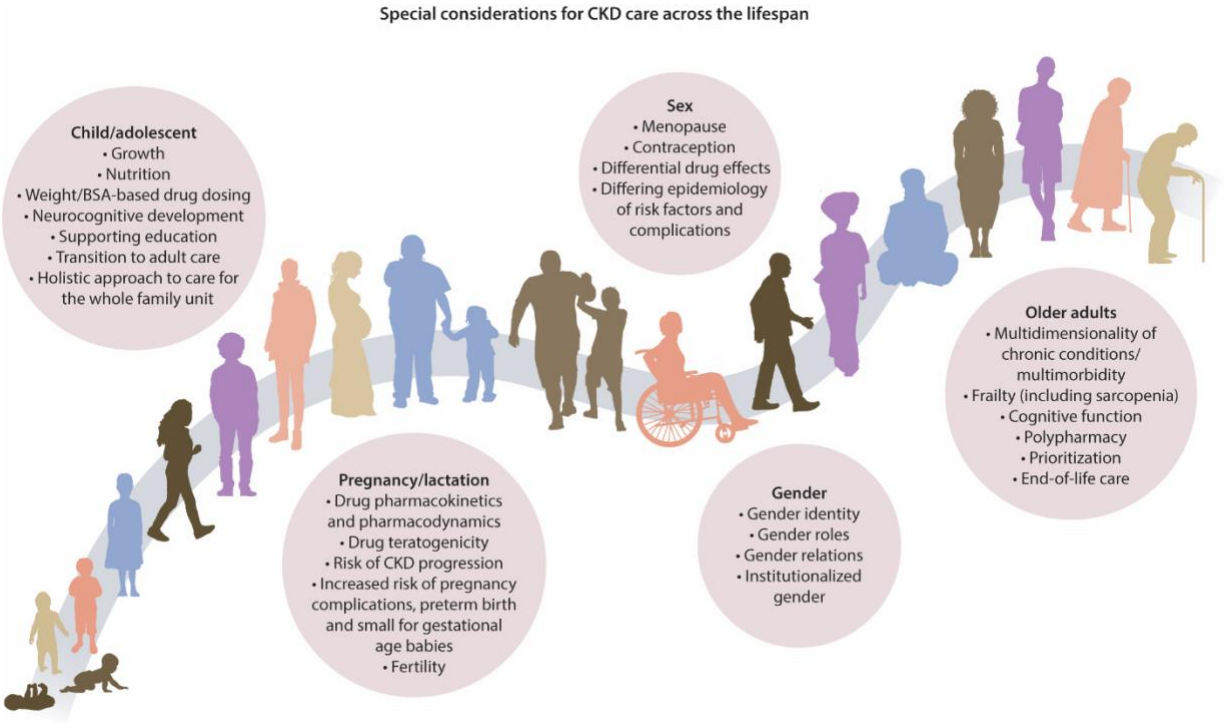


Figure 3. Special considerations for chronic kidney disease (CKD) care across the lifespan. BSA, body surface area

Delivery of care

Pediatric healthcare providers engage with not only the person with CKD, but also their carers and siblings. Age-appropriate care and education, understood by both the child and their carers, is necessary. Holistic consideration of the needs and capabilities of the family unit is important in ensuring effective CKD care. Engagement with patients and families must change over the course of childhood from being entirely carer-directed for infants, changing to include the whole family unit in childhood, and then leaning toward the young person to ensure successful transition to adult-oriented care.

Growth, puberty, and young adulthood

Childhood and adolescence are characterized by physical growth and development. All CKD care aims to optimize this physiological process, which is commonly disrupted by CKD. Puberty is a time of rapid somatic growth with an increase in muscle bulk, and therefore constitutes a high-risk period for CKD progression as compromised kidneys may not hypertrophy to adapt to the larger body size. Adolescence and emerging adulthood brings individuation, exploration of sexuality and adult behaviors, and kidney disease care must recognize and adapt to these changes.

Kidney development and long-term assessment of kidney risks

While nephron formation is complete by 36 weeks gestation, kidney function continues to develop throughout early childhood, with nephron growth and maturation progressing

particularly rapidly in the first year of life. An increase in GFR over the course of the first 1-2 years of life, and even up to 4 years of age, is expected. A trajectory of increasing GFR in infancy and very early childhood followed by a period of relative stability and a subsequent progression in CKD in adolescence or adulthood is common. Given the long life expectancy of children, follow-up plans must take into account the risk of late CKD or kidney failure. Healthy children and adolescents should have excellent kidney function, so an estimated glomerular filtration rate (eGFR) under 90 ml/min per 1.73 m^2 (CKD G2–G5) represents decreased kidney function in these age groups. Early assessment and intervention of children with CKD is crucial to maximize overall health across the lifespan.

Neurodevelopment and education

The primary goal of pediatric CKD care is to optimize neurodevelopmental gains. CKD can affect development, cognition, school attendance, vocational outcomes, and future employment. Mitigating these deficits through effective, individualized care is essential to give children with CKD the best possible future.

Considerations in older adults

Older adults constitute a substantial and steadily growing proportion of people under nephrology and medical care globally, especially in Western industrialized countries. Longevity in many parts of the world is increasing, and thus the prevalence of CKD in those people is also increasing: The 2022 US Renal Data System (USRDS) annual data report highlights that the number of individuals initiating KRT is continuously ascending with increasing age. In Taiwan, for example, KRT incidence in those aged 75+ was 2858 per million population (pmp) compared to 1583 pmp among people aged 65-74 years, 530 pmp among people aged 45-64 years, and 97 pmp among people aged 20-44 years. The pattern is very similar across the globe with the majority of people initiating dialysis over the age of 75 which puts emphasis on a group of people who are not just old, but very old, and incorporates more and more people over the age of 80. Octo- and nonagenarians often demonstrate distinct patterns of disease complexity. These features include multimorbidity often accompanied by polypharmacy, frailty, cognitive impairment, and geronto-psychiatric disorders among others. Often, several of these features coexist especially in older adults with CKD.

Implications for aging adults with CKD are important in both diagnosis and treatment. The interpretation of laboratory results (specifically SCr) used in the staging system should factor in an older adult's habitus given the frequency of sarcopenia. A creatinine-based eGFR will overestimate GFR in the elderly (and others) with sarcopenia leading to drug overdosing. Urine albumin-to-creatinine ratio (ACR) at the same time will be falsely high due to the falsely low creatinine in the denominator. Furthermore, the presence of frailty may alter treatment targets recommended for younger people with CKD, as they may not necessarily be transferable to older adults. Strict BP-lowering, for example, may come with the risk of

dizziness and falls in older adults, many of whom are on anticoagulants risking severe hemorrhage.

The multidimensionality of comorbidities in old age poses challenges, as it demands a sophisticated integrated and complex multidisciplinary care and treatment approach, which may not be available in every healthcare system. Life expectancy in old age is naturally limited compared to younger people. Perspectives and treatment goals shift over the life course, and recognizing these in very old adults, as different from those in middle-aged or younger adults with CKD, is critical to the development of more personalized care plans and goals. Specifically, pure survival may become less of a priority for an older individual, whereas maintaining an acceptable, good quality of life may be more important. The context of a person's situation and own values and preferences may modify the prioritization for testing, treatment types, and treatment goals. For example, the decision-making between KRT and conservative care should be made on the basis of the person's priorities, medical needs, and informed decision as to benefits and harms of various options. These informed decisions require good communication between caregivers, people with CKD, and their relatives/carers; they require time, "room", adequate understandable language, patience, trust, and commitment. Repeated conversations are critical, given the higher prevalence of cognitive deficits in older adults with CKD. These cognitive issues accompany both aging and CKD and frequently remain unrecognized; thus, impeding shared decision-making and advance care planning in this group.

In summary, older adults constitute the largest group among all people with advanced CKD. While every single person needs individual care, the multidimensional medical complexity inherent in very old age is challenging. Where specific recommendations or practice points require special consideration in the elderly, we make clear statements in the special considerations section.

Considerations regarding sex and gender

It is increasingly recognized that sex (biological attributes) and gender (sociocultural factors) differences across individuals contribute to differences in kidney health and disease.[29] Sex-based variation in genetics, physiology, immunology and anatomy, as well as gender factors such as identity, roles, and relations in addition to institutionalized gender influence kidney disease pathophysiology, presentation, response to therapy, complications, and outcomes, highlighting the need to take these factors into consideration in the care of the person living with kidney disease.

Globally, the prevalence of CKD not being treated with dialysis defined by level of eGFR is greater in women compared to men.[30] Progression of CKD has been reported as more rapid in men,[31] in women,[32, 33] or no difference by sex or gender.[34] These incongruities are

likely a reflection of differences in cause of kidney disease and definitions of outcomes (e.g., loss of eGFR or receipt of KRT).

There is substantial literature demonstrating that both sex-related factors (e.g., puberty, menstrual patterns, hormonal contraception, pregnancy and pregnancy-related complications, menopause, menopausal hormone therapy, testosterone levels, and gender-affirming hormone therapy) and gender-related factors (e.g., prescription of and adherence to medications and diet, access to and follow-up with health care providers, and decision-making around KRT) play important roles in the risk, progression, complications, and treatment of kidney disease.[35]

These factors will play prominent roles in progression of kidney disease across different stages of the life cycle. For example, use of some recommended medications has not been studied in pregnant populations, highlighting the importance of contraceptive counselling in accordance with a person's values and preferences. In other instances, preconception counselling, changing medications to nonteratogenic options and a multidisciplinary approach is required to optimize the outcomes of a potential pregnancy in the setting of CKD. Sex-based differences in pharmacokinetics and pharmacodynamics that are accentuated with increasing age and changing hormonal status may alter the response to different therapies for the treatment of kidney disease. For example, women are more likely to report adverse reactions to angiotensin-converting enzyme inhibitors (ACEi),[36] which plays a role in adherence and failure to reach guideline-recommended target doses.

There are differences between women and men in the detection, recognition, monitoring, referrals, and management of CKD.[37, 38] While the reasons behind these disparities are unclear, access to kidney care may be limited by familial and other caregiving responsibilities, as well as financial challenges, occupational obligations, and time constraints which are influenced by gender identity (how an individual self-identifies, behaves, expresses their gender, and is perceived by others; e.g. woman, man, girl, boy, gender-diverse), roles (social expectations and norms typically associated with a given gender; e.g., primary household earner, caregiver), relations (interactions with and treatment by others based on an individual's perceived and/or expressed gender identity) and institutionalized gender (e.g., distribution of power and resources in society).[29]

A small but increasing proportion of the world's population identifies as transgender, gender-diverse or non-binary where sex assigned at birth differs from gender identity, highlighting the urgent need to build transgender cultural safety within all aspects of kidney disease management and care.[39]

Taking sex and gender considerations into account is critical to optimize the care of the individual with kidney disease. While there is increasing literature to inform sex- and gender-

specific recommendations in nephrology, significant knowledge gaps remain, underscoring the importance of a person-centered approach in kidney care.

SUMMARY OF RELATIVE AND ABSOLUTE RISKS RELEVANT TO CKD FROM CATEGORICAL META-ANALYSIS OF LARGE MULTINATIONAL POPULATION STUDIES IN THE CKD PROGNOSIS CONSORTIUM (CKD-PC)

Outcomes relevant to CKD, and the prognostic importance of CKD categories

The most highly evaluated endpoints in epidemiological studies have been all-cause mortality, cardiovascular events (myocardial infarction, stroke, and heart failure), and kidney-specific outcomes (progression to kidney failure, AKI), although additional outcomes such as all-cause hospitalization and incident atrial fibrillation have been studied more recently. In this section, we highlight newer data derived from CKD Prognosis Consortium.[40] We describe the associations of CKD categories with 10 of these important outcomes and demonstrate the importance of different methods of estimating GFR (i.e., using creatinine- or cystatin C-based equations), on these risk gradients.

Healthcare providers, researchers, and policy makers should understand the association of CKD parameters (ACR and eGFR) on populations. The overall distributions of **epidemiological risk across CKD categories on a population level** are presented here. This is not to be confused with the information presented in Chapter 2, where **individualized risk assessment tools are described**, and those tools can be used to inform clinical and management decisions for individual people with CKD.

Associations of all complications of CKD are incrementally increased with worsened categories of estimated glomerular filtration rate (eGFR) and albuminuria: updated data.

The *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* introduced the combined staging by eGFR and albuminuria categories, which were justified by their associations with CKD complications.[1] The combined associations of eGFR and ACR categories were presented as "heatmaps", a color-coded depiction of the associations of increased risk with worsening CKD, for outcomes of all-cause mortality, kidney failure, AKI, and cardiovascular mortality on a population level. In this section, we provide an update to these CKD heatmaps which have been provided by the CKD Prognosis Consortium.[40]

Several changes in the development of these updated heatmaps are important to highlight.

1. They now include several clinical databases which allow a much larger population base, comprising up to 27,503,140 people for the analyses of each adverse outcome.
2. The creatinine-based eGFR (eGFRcr) has been changed to the 2021 CKD Epidemiology Collaboration (CKD-EPI) equation, as this newer version no longer includes race as a component.

3. The number of outcomes has been increased to 10: including 6 that are cardiovascular related, 2 that are kidney specific (kidney failure and AKI), and 2 general outcomes (all-cause mortality and all-cause hospitalization).
4. Additional analyses have been conducted using the 2021 CKD-EPI combined eGFR equation that incorporates both creatinine and cystatin C. Although the sample size for these subsequent analyses is much smaller (n=692,802**)**, it does permit better differentiation of associations of eGFR and risk and allows validation of CKD thresholds across populations.

CKD staging by eGFRcr and ACR and association with adverse events

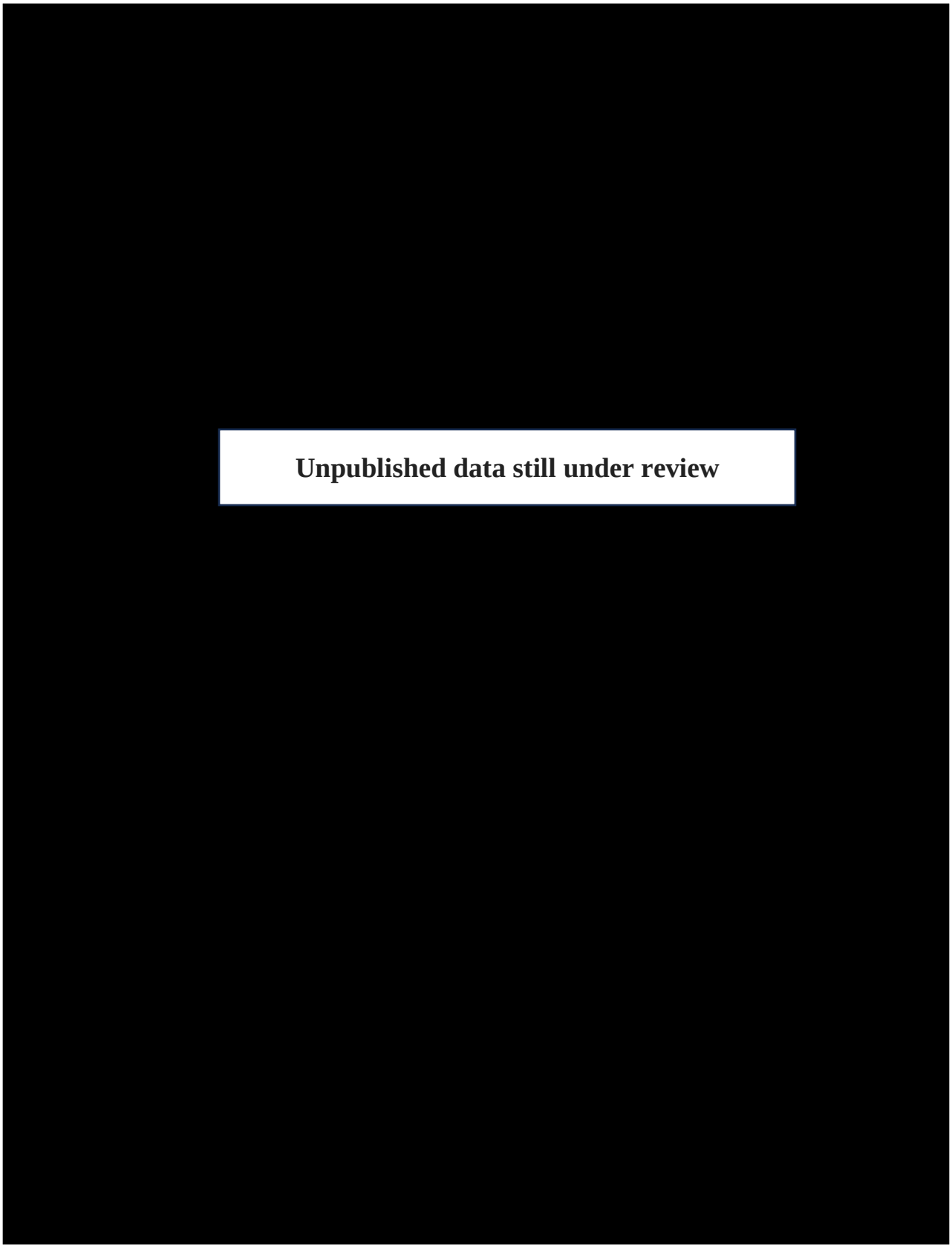
Figure 4a-j present the relative risks for all eGFR/ACR combinations for the 10 identified outcomes.

The relative risks presented have all been adjusted for age, sex, smoking status (current, former, never), systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol, body-mass index (BMI), use of antihypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease. **Therefore, the relative risks can be interpreted as the proportional elevation in risk for each outcome experienced by people in that stage of CKD (or non-CKD) compared to people in the healthiest group.** Across all the heatmaps, a consistent color scheme is used.

The figures reveal several common themes and highlight the necessity of having both eGFR and ACR parameters available in assessing risk. First, within the CKD population, the association of risk for all 10 outcomes increases with higher stages of both eGFR and albuminuria. The figures present only the **relative risks for each specific stage and not the absolute risk of experiencing that outcome for people in the risk cell**. This distinction between relative and absolute risks demonstrates the importance of using individual risk prediction tools for persons with CKD, a subject of Chapter 2.

Although nearly all CKD categories are at substantially elevated risk for most outcomes in Figures 4a-j, a distinction must be made for people in the eGFRcr CKD G3a and with the lowest ACR severity (<10 mg/g). This group is portrayed in the lower-risk green color for 7 of the 10 outcomes presented, although they have 3-fold higher adjusted risk of AKI and 13-fold higher risk of kidney failure compared with the reference group. The inconsistent risk association for populations with CKD G3a, A1, particularly in older adults, has led to controversy over whether this group should be considered as having CKD.[41] The CKD-PC investigators repeated all 10 heatmaps using creatinine and cystatin C-based eGFR (eGFRcr-cys), in part to evaluate whether the weaker associations of CKD G3a, A1 with clinical outcomes were caused by the limitations of the specific creatinine-based equation eGFRcr,

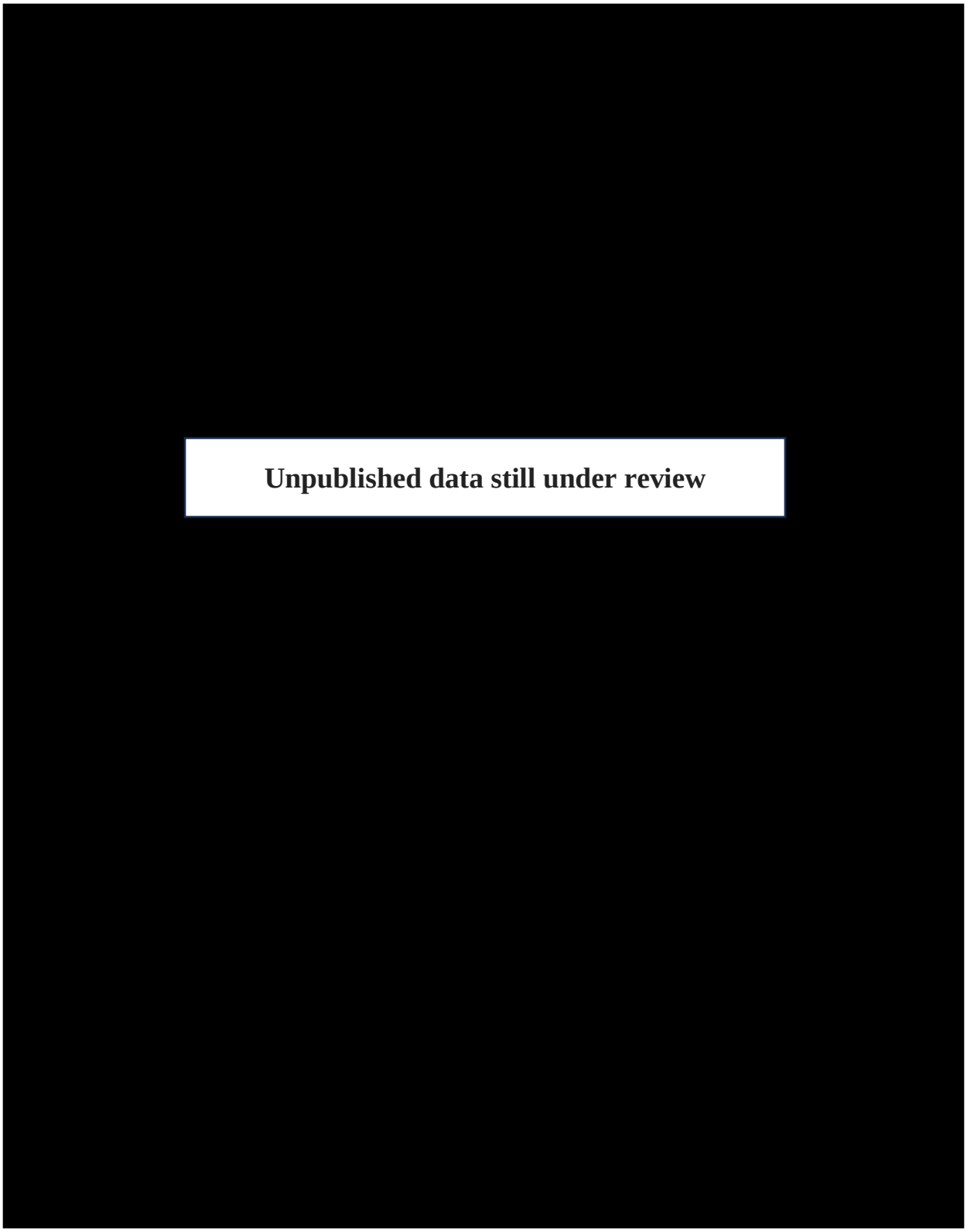
compared with eGFRcr-cys which has been established as a better approximation of measured GFR (mGFR) than creatinine-based eGFR (Figure 5a-j).


Unpublished data still under review

Figures 4a-j: Associations of CKD staging by estimated glomerular filtration rate by creatinine (eGFRcr) and albumin-to-creatinine ratio (ACR) categories and risks for 10 common complications in multivariable-adjusted analyses.

CKD staging by eGFRcr-cys and ACR and risk for adverse events

Within the CKD-PC collaboration, 692,802 individuals had measures of blood cystatin C in addition to having eGFRcr and ACR. The replacement of eGFRcr with eGFRcr-cys in the heatmap led to several changes in the risk distributions. **Most notably, the group with eGFR category 45-59 ml/min per 1.73 m^2 and ACR <10 mg/g were moved to higher risk for all 10 outcomes**, and this cell was no longer labeled green for any of the complications (Figures 5a-j**)**. The distinction in these risk relationships was further explored using spline analyses to depict the risk relationships of eGFRcr and eGFRcr-cys with all the 10 complications. For the 8 outcomes that are not influenced by changes in creatinine (all except kidney failure and AKI), eGFRcr exhibited a J-shaped association such that risk increased with eGFR values over 105 ml/min per 1.73 m^2 (Figure 6). **In contrast, eGFRcr-cys demonstrated much more linear associations with each of these complications throughout its distribution.**



Figures 5a-j: Associations of CKD staging by estimated glomerular filtration rate by creatinine and cystatin C (eGFRcr-cys) and albumin-to-creatinine ratio (ACR) categories and risks for 10 common complications in multivariable-adjusted analyses.

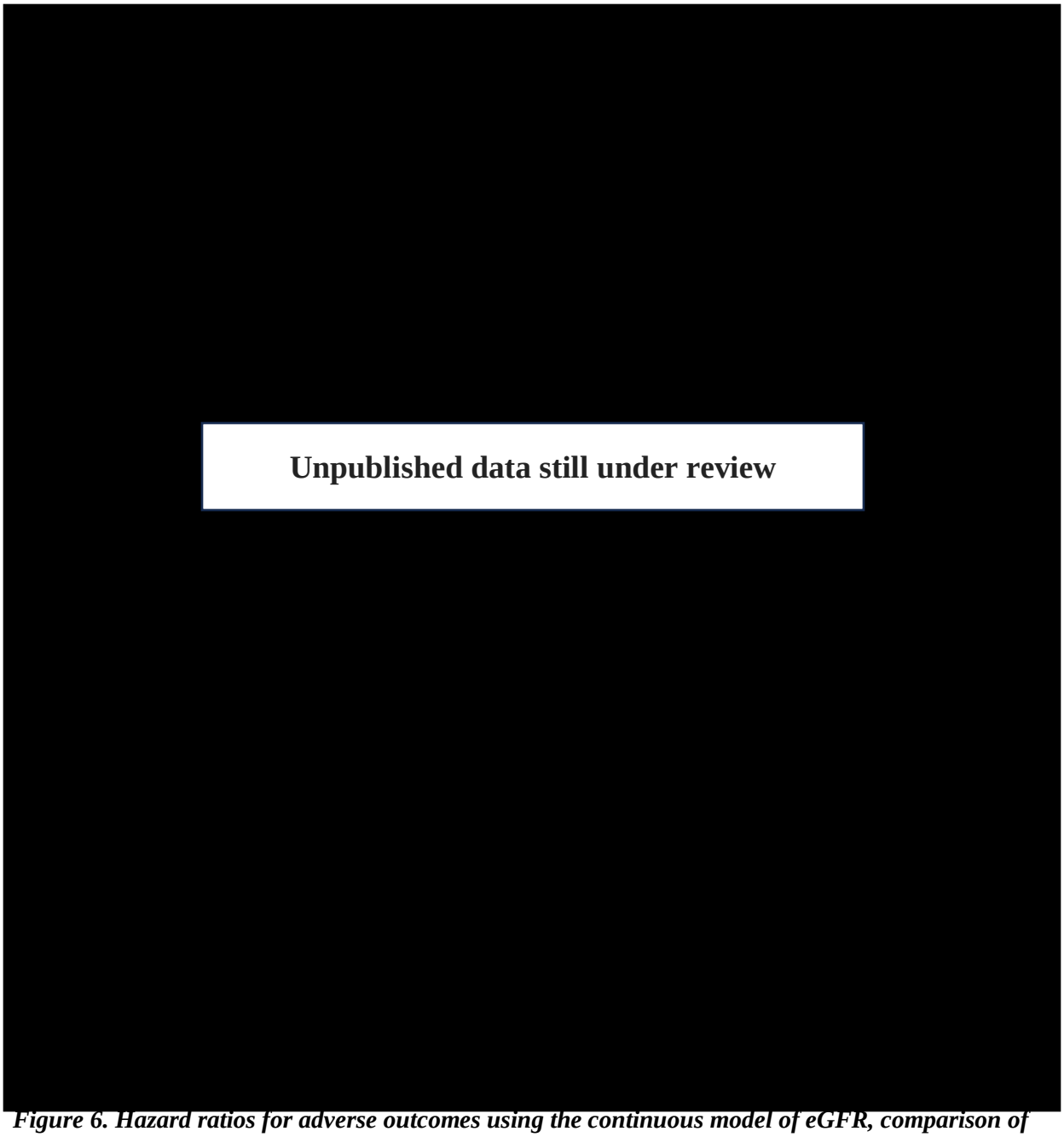


Figure 6. Hazard ratios for adverse outcomes using the continuous model of eGFR, comparison of the shape of associations between eGFRcr and eGFRcr-cys in the population with cystatin C (eGFRcr-cys population). ACM, all-cause mortality; CVM, cardiovascular mortality; HOSP, all-cause hospitalizations; MI, myocardial infarction; HF, heart failure; AF, atrial fibrillation; PAD, peripheral artery disease.

Based upon the risk relationships of eGFRcr-cys and ACR categories with all complications, the existing CKD staging is appropriate among both younger and older adults.

Some authors have suggested that the GFR threshold for CKD of 60 ml/min per 1.73 m^2 should be raised to 75 ml/min per 1.73 m^2 for younger adults and lowered to 45 ml/min per 1.73 m^2 for older adults.[41] In younger adults, the purpose of a higher GFR threshold reflects the

longer risk horizon for younger people, which could lead to higher lifetime CKD progression risks for a given GFR stage. However, the higher lifetime progression risks in younger adults with GFR 60–89 ml/min per 1.73 m^2 can be addressed in their management without changing the definition of CKD. Efforts should be directed at people with higher risk with GFR levels >60 ml/min per 1.73 m^2 to prevent the incidence of CKD or further reductions in GFR.

Among older adults, the findings of consistently elevated relative risk for older adults with CKD G3a, A1, as defined by eGFRcr-cys, support the inclusion of this large group in the CKD population. These elevated relative risks tell us how much more likely the outcome is compared to the reference group (eGFR 90–104 ml/min per 1.73 m^2 and ACR <10 mg/g). Crucially, they don't tell us what the overall likelihood of the outcome, the absolute risk, is. The **absolute risk** for important CKD complications is higher among older than younger adults at nearly every stage, particularly for cardiovascular disease, heart failure, and mortality. Therefore, this population is also likely to benefit from having their CKD diagnosed, staged, and treated.

Rationale for using cystatin C containing equations for CKD staging

The rationale for using cystatin C versus SCr, or a combination of both, in eGFR equations is that creatinine, which is directly linked to muscle mass, may be misleading at extremes of body habitus, or in specific conditions (spinal cord injuries, sarcopenia), and that cystatin C is impacted by different variables (steroid use, thyroid disease, cancer). Thus, since neither is a perfect marker to use for estimating clearance, the combination of the 2 compounds gives more accurate estimates of GFR when compared to measured values.

Very low levels of SCr often represent poor health status, such as frailty or sarcopenia, which limit the production of SCr. This biological feature of SCr (i.e., relation to muscle mass) has limited its prognostic utility, and results in reducing the risk associations for eGFRcr 45-60 ml/min per 1.73 m^2 and elevating risks for eGFRcr >110 ml/min per 1.73 m^2. These limitations are not observed when risk is estimated using eGFRcr-cys or cystatin C-based eGFR (eGFRcys) (Figure 6).

Comparing GFR estimates using these 2 filtration markers, risk gradients are consistently stronger for most outcomes for eGFRcys in comparison with eGFRcr. Therefore, for the purpose of evaluating the association of eGFR with outcomes (i.e., projecting prognosis for people with CKD), the eGFRcys or eGFRcr-cys can be considered most accurate.

SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

CHAPTER 1. EVALUATION OF CKD

1.1. 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 either elevated albumin-to-creatinine ratio (ACR) or low estimated GFR (eGFR), repeat both urine albumin and eGFR 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 that 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]); or if unavailable, use creatinine-based estimated glomerular filtration rate (eGFRcr) (1B).

1.1.3. Evaluation of chronicity

Practice Point 1.1.3.1: Proof of chronicity (duration 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 as acute kidney injury (AKI) can present with eGFR and ACR abnormalities in the context of subtle clinical symptoms, and yet be due to an acute event/condition.

Practice Point 1.1.3.3: Consider initiation of treatments for CKD at initial identification if chronicity is deemed likely.

1.1.4. Evaluation of cause

Practice Point 1.1.4.1: Establish the etiology in all people identified as having CKD using clinical context, personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis (Figure 7).

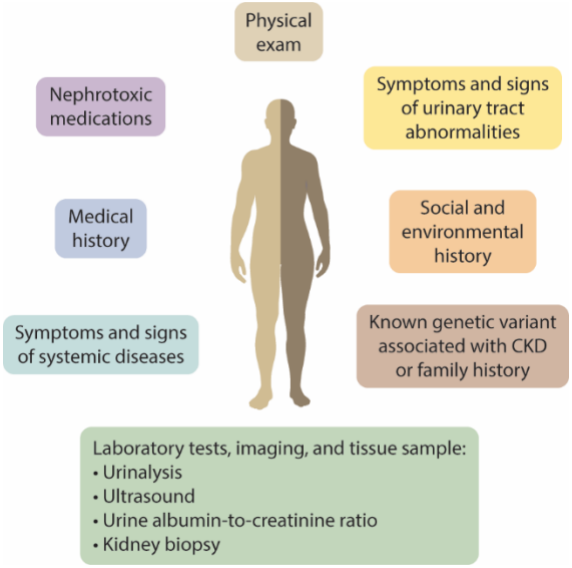


Figure 7. Evaluation of cause. CKD, chronic kidney disease

Practice Point 1.1.4.2: Use tests to establish a cause based on resources available (Table 7).

Test category	Examples	Comment or key references
Imaging	Ultrasound, intravenous urography, CT kidneys ureters bladder, nuclear medicine studies	Assess kidney structure (i.e., kidney shape, size, symmetry, and evidence of obstruction) for cystic disease, reflux disease. Evolving role of additional technologies (e.g., 3D ultrasound)
Kidney biopsy	Ultrasound guided percutaneous	Usually examined by light microscopy, immunofluorescence, and electron microscopy, and, in some situations, may include molecular diagnostics Used for exact diagnosis, planning treatment, assessing activity and chronicity of disease, and likelihood of treatment response; may also be used to assess genetic disease
Laboratory tests	PLA2R, ANCA, anti-glomerular basement membrane antibodies Serum free light chains, serum and urine protein electrophoresis/immunofixation	Refer to *KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases*[18] Increasing recognition of the role of light chains in kidney disease even in the absence of multiple myeloma (monoclonal gammopathy of renal significance [MGRS])[42]
Genetic testing	APOL1, COL4A, NPHS1, TRPC6	Evolving as a tool for diagnosis, increased utilization is expected. Recognition that genetic causes are more common and might be seen without classic family history.[43]

Table 7. Guidance for selection of additional tests for evaluation of cause. ANCA, antineutrophil cytoplasmic antibody; CT, computed tomography; PLA2R, M-type phospholipase A2 receptor

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).

1.2. Evaluation of GFR

1.2.1. Other functions of kidneys 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.

1.2.2. Evaluation of GFR: 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 (Figure 8).

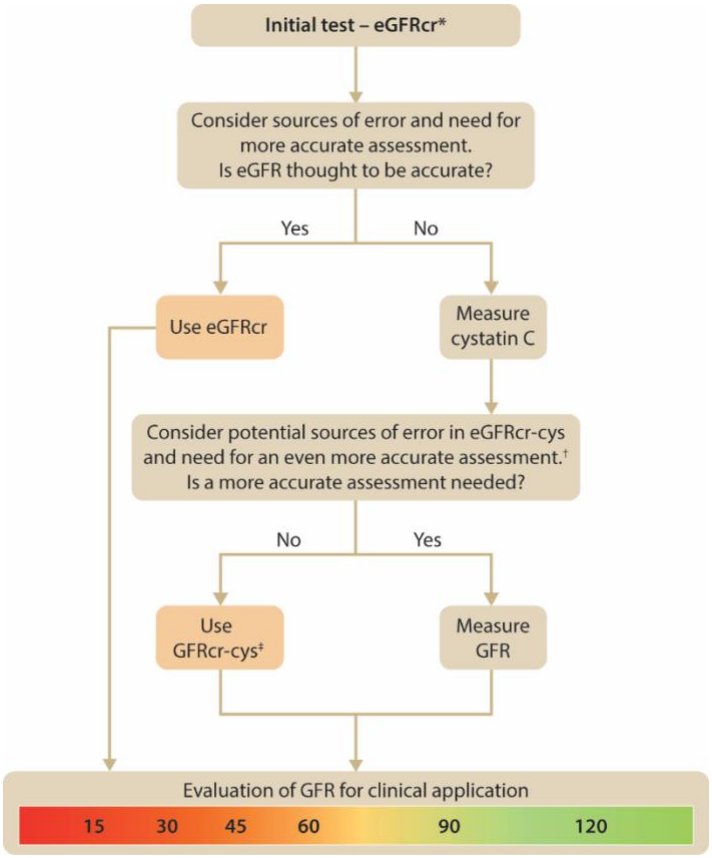


Figure 8. Approach to glomerular filtration rate (GFR) evaluation using initial and supportive tests.
The algorithm describes the approach to the evaluation of GFR. Our approach is to use initial and supportive testing to develop a final assessment of true GFR and to apply it in individual decision-making. The initial test for evaluation of GFR is creatinine-based estimated GFR (eGFRcr), which will be available in most people because creatinine is measured routinely as part of the basic metabolic panel. If eGFRcr is expected to be inaccurate, or if a more accurate assessment of GFR is needed for clinical decision-making, such as diagnosis or staging of CKD or drug dosing, then cystatin C should be measured, and creatinine and cystatin C-based estimated GFR (eGFRcr-cys) should be estimated. If eGFRcr-cys is expected to be inaccurate, or if an even more accurate assessment of GFR is needed for clinical decision-making, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. *Initial test may be estimated GFR by cystatin C (eGFRcys or eGFRcr-cys) in in otherwise healthy populations with changes in creatinine generation due to nonGFR determinants such as changes in muscle mass or creatinine secretion or extrarenal elimination due to use of specific medications. †Sources of error in eGFRcr-cys include very low muscle mass or very high levels of inflammation, high catabolic states, exogenous steroid use. ‡Consider eGFRcys rather than eGFRcr-cys in otherwise healthy populations with decreased creatinine generation due to reduced muscle mass or decreased creatinine secretion or extrarenal elimination due to use of specific medications

Recommendation 1.2.2.1: We recommend using eGFRcr-cys in clinical situations when eGFRcr is less accurate and GFR affects clinical decision-making (Table 9) (1C).

Domain	Specific clinical condition	Cause of decreased accuracy	Comments on GFR evaluation
Body habitus and changes in muscle mass	Anorexia nervosa[44]	nonGFR determinants of SCr	eGFRcys may be appropriate if no comorbid illness other than reduction in muscle mass
	Extreme sport/exercise/body builder	nonGFR determinants of SCr	eGFRcys may be appropriate if increase in muscle mass is the only abnormality
	Above knee amputation[45]	nonGFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid conditions Suggest eGFRcr-cys in those with comorbid illness
	Spinal cord injury with paraplegia/paraparesis or quadriplegia/quadriparesis	nonGFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid illness Suggest eGFRcr-cys in those with comorbid illness
	Class III obesity (BMI>40 kg/m^2)†	nonGFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate
Lifestyle	Smoking[46-48]	nonGFR determinants of SCys	Minimal data, suggest eGFRcr if no changes to nonGFR determinants of SCr or comorbid illness
Diet	Low protein diet	nonGFR determinants of SCr	Minimal data, suggest eGFRcys may be appropriate if no changes to nonGFR determinants of SCr or comorbid illness
	Keto-diets	nonGFR determinants of SCr	
	Vegetarian	nonGFR determinants of SCr	
	High protein diets and creatine supplements	nonGFR determinants of SCr	
Illness other than CKD	Malnutrition	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys because of coexistence of malnutrition and inflammation Suggest using mGFR for treatment decisions based on level of GFR

	Cancer[†49-51]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail people or in cancers with high cell turnover. Suggest using mGFR for treatment decisions based on level of GFR
	Heart failure[†52]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys highly inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Cirrhosis[†]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys highly inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Catabolic consuming diseases[*]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	Minimal data but eGFRcr-cys may be inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Muscle wasting diseases	nonGFR determinants of SCr	Suggest eGFRcys in those without other comorbid illness eGFRcr-cys in those with other comorbid illness
Medication effects	Steroids (anabolic, hormone)	nonGFR determinants of SCr. Effect on SCys not known	Physiological effect on SCys unknown, suggest eGFRcr-cys
	Decreases in tubular secretion	nonGFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness. Suggest using mGFR for treatment decisions based on level of GFR
	Broad spectrum antibiotics that decrease extrarenal elimination	nonGFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness Suggest using mGFR for treatment decisions based on level of GFR

Table 9. Indications for measurement of cystatin C. eGFR, estimated glomerular filtration rate; eGFRcr-cys, creatinine and cystatin C-based estimated GFR, eGFRcr, creatinine-based estimated GFR; GFR, glomerular filtration rate; SCr, serum creatinine; SCys, serum cystatin C. [*]Catabolic

consuming disease may include tuberculosis (TB), acquired immune deficiency syndrome (AIDS), hematologic malignancies, severe skin diseases. There is no data with measured glomerular filtration rate (mGFR) to evaluate this directly. †Data summarized in Adingwupu et al.[53]

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 (Table 10).

Estimated GFR by SCr and/or cystatin C	Measured GFR
Inexpensive and easy to implement	More expensive, more time-consuming, and invasive
Widely available and may also be used at point of care, easily repeatable	Only available in certain centers Microsampling tests by fingerpick enables point-of-care testing
Not sufficiently accurate and precise for all clinical situations	Accurate for GFR in all situations and across the GFR range
Lags behind changes in GFR	Able to identify early changes in GFR
Subject to nonGFR determinant confounding	Not subject to nonGFR determinants

Table 10. Comparison of estimated glomerular filtration rate (GFR) and measured GFR. SCr, serum creatinine

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: Wait at least 12 hours before measurement of SCr, following meat or fish 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: Cystatin C-based estimated glomerular filtration rate (eGFRcys) may be indicated 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 if mGFR is not available and eGFRcr-cys is thought to be inaccurate.

1.2.3. Evaluation of GFR: Clinical laboratories

Practice Point 1.2.3.1: Implement the laboratory standards of care outlined in Table 12 to ensure accuracy and reliability when assessing GFR using creatinine and cystatin C.

• Report eGFR in addition to the serum concentrations of filtration markers using valid equations.
• Report eGFR rounded to the nearest whole number and relative to a body surface area (BSA) of 1.73 m^2 in adults using the units ml/min per 1.73 m^2.
• Reported eGFR levels <60 ml/min per 1.73 m^2 should be flagged as being low.
• When reporting levels of filtration markers, report (i) SCr concentration rounded to the nearest whole number when expressed as standard international units (µmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl). (ii) serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/l).
• Measure filtration markers using a specific, precise (coefficient of variation [CV] <2.3% for creatinine and <2.0% for cystatin C) assay with calibration traceable to the international standard reference materials and desirable bias (<3.7% for creatinine, <3.2% for cystatin C) compared to reference methodology (or appropriate international standard reference method group target in external quality assessment [EQA] for cystatin C).
• Use an enzymatic method to assay creatinine.
• Process blood for creatinine by the laboratory within 12 hours of venipuncture.
• When cystatin C is measured, measure creatinine on the same sample to enable calculation of eGFRcr-cys

Table 12. Implementation standards to ensure accuracy and reliability of glomerular filtration rate assessments using creatinine and cystatin C. eGFR, estimated glomerular filtration rate; eGFRcr-cys, estimated glomerular filtration rate based on creatinine and cystatin C; SCr, serum creatinine

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 over the age of 2 years.

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). Within such regions, equations may differ for adults and children.

Practice Point 1.2.4.2: Use of race as a distinct variable 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.

1.3. 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 mid-stream sample is preferred in adults and children.

1. **urine ACR**
2. **urine protein-to-creatinine ratio (PCR)**
3. **reagent strip urinalysis for albumin and ACR with automated reading**
4. **reagent strip urinalysis for total protein with automated reading**
5. **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 mid-stream 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 (Table 17).

	Factor	False positive	False negative
Variability in urine albumin or protein	Hematuria	Increases albumin and protein in the urine	
	Menstruation	Increases albumin and protein in the urine	
	Exercise[54]	Increases albumin more than other proteins in the urine	
	Infection[55, 56]	Symptomatic urinary infection can cause production of protein from the organism.	
	Non-albumin proteins		Other proteins may be missed by albumin reagent strips
Variability in urinary creatinine concentration	Biological sex	Females have lower creatinine excretion, therefore higher ACR.	Males have higher creatinine excretion, therefore lower ACR.
	Weight[57, 58]	High creatinine excretion consistent with high weight can cause low ACR or PCR relative to timed excretion	Low creatinine excretion consistent with low weight can cause high ACR or PCR relative to timed excretion
	Changes in creatinine excretion	Lower urinary creatinine concentration with AKI	Increased urinary creatinine concentration with meat intake or exercise

Table 17. Factors causing biological variation in urine albumin or urine protein. ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; PCR, protein-to-creatinine ratio

Special considerations

Pediatric considerations

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

1. **urine PCR**

2. **urine ACR**
3. **reagent strip urinalysis for total protein with automated reading**
4. **reagent strip urinalysis for total protein 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 Table 18 to ensure accuracy and reliability of the findings when assessing urine samples.

• Samples analyzed fresh or stored at 4ºC for up to 7 days.
• Samples should not be stored frozen at -20ºC.
• Report ACR in untimed urine samples in addition to urine albumin concentration rather than the concentrations alone.
• Reporting to one decimal place for ACR whether mg/mmol or mg/g
• Analytical CV of methods to measure urine albumin should be <15%.

***Table 18. Implementation standards to ensure accuracy and reliability of urine samples*.** ACR, albumin-to-creatinine ratio; CV, coefficient of variation

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

1.4. 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 that is 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 95% of people with significant albuminuria (ACR ≥30 mg/g or ≥3 mg/mmol), as part of the evaluation and consideration of using the device.

CHAPTER 2. RISK ASSESSMENT IN PEOPLE WITH CKD

2.1. Overview on monitoring for progression of CKD based upon GFR and ACR categories

Practice Point 2.1.1: Assess albuminuria in adults, or 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.

2.2. 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 predication 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 prediction equations in patients with immunoglobulin A nephropathy (IgAN) and autosomal dominant polycystic kidney disease (ADPKD).

2.3. 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 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 models that predict all-cause mortality that are developed in the CKD population.

CHAPTER 3. DELAYING CKD PROGRESSION AND MANAGING ITS COMPLICATIONS

3.1. CKD treatment and risk modification

Practice Point 3.1: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications (Figure 14).

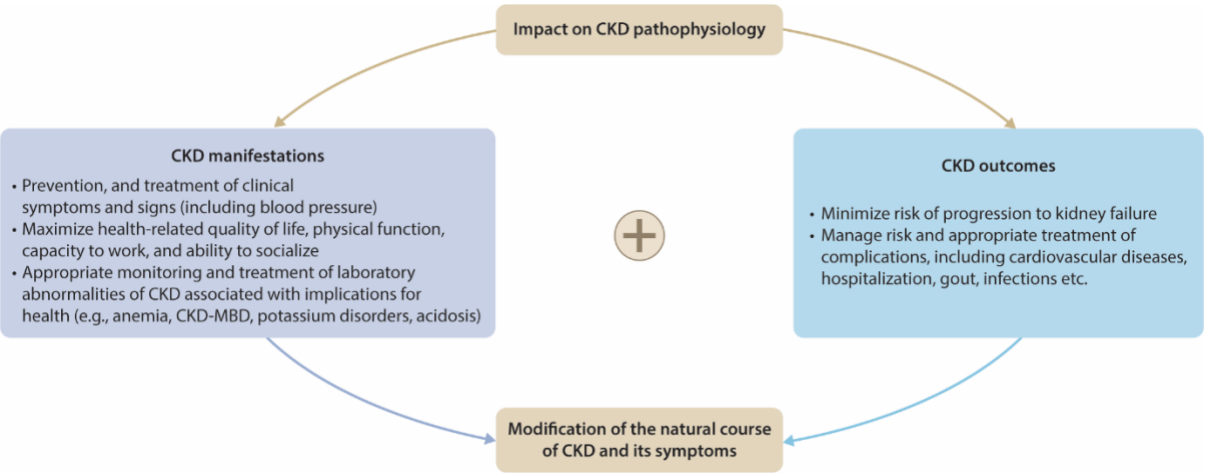


Figure 14. Chronic kidney disease (CKD) treatment and risk modification. CKD-MBD, chronic kidney disease-mineral and bone disorders

3.2. 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, dieticians, physical and occupational therapy, and smoking cessation programs) should be offered where indicated and available.

3.2.1. Avoiding use of tobacco products

[No recommendations or practice points]

3.2.2. Physical activity and optimum weight

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

Practice Point 3.2.2.3: People with CKD should be advised to avoid sedentary behavior.

Practice Point 3.2.2.4: 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 3.2.2.5: Physicians should consider advising/encouraging people with obesity and CKD to lose weight, particularly people with eGFR ≥30 ml/min per 1.73 m^2.

Special considerations

Pediatric considerations

Practice Point 3.2.2.6: 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.

3.3. 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 registered dieticians or accredited nutrition providers to provide information for 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, where available.

3.3.1. Protein intake

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

Practice Point 3.3.1.1: Do not restrict protein intake in adults with sarcopenia, cachexia, or conditions that result in undernutrition.

Practice Point 3.3.1.2: Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.

Special considerations

Pediatric considerations

Practice Point 3.3.1.3: 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.

3.3.2. Sodium intake

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 not appropriate for patients with sodium-wasting nephropathy.

Special considerations

Pediatric considerations

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

3.4. Blood pressure control

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: We suggest monitoring BP once a year with ABPM and monitoring 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.

3.5. Renin-angiotensin system inhibitors

Recommendation 3.5.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (1B).

Recommendation 3.5.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (2C).

Recommendation 3.5.3: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).

Recommendation 3.5.4: 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 3.5.1: 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 3.5.2: 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 3.5.3: 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 3.5.4: 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 3.5.5: 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 3.5.6: Consider starting people with CKD with mildly increased albuminuria (A1) with RASi (ACEi or ARB) for specific indications (e.g., to treat hypertension or heart failure with low ejection fraction).

Practice Point 3.5.7: Continue ACEi or ARB in people with CKD even when the eGFR falls below 30 ml/min per 1.73 m^2.

3.6. Sodium--glucose contransporter-2 inhibitors (SGLT2i)

Recommendation 3.6.1: 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 3.6.1: 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 3.6.2: 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 3.6.2: We recommend treating adults with CKD and heart failure or eGFR ≥20 ml/min per 1.73 m^2 with urine albumin-to-creatinine ratio (ACR) ≥200 mg/g with an SGLT2i (1A).

Practice Point 3.6.3: 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 3.6.3: We suggest treating adults with eGFR ≥20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g with an SGLT2i (2B).

3.7. Mineralocorticoid receptor antagonists (MRAs)

Recommendation 3.7.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an 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 3.7.1: 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 3.7.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.7.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 22).

Practice Point 3.7.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 3.7.5: 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.

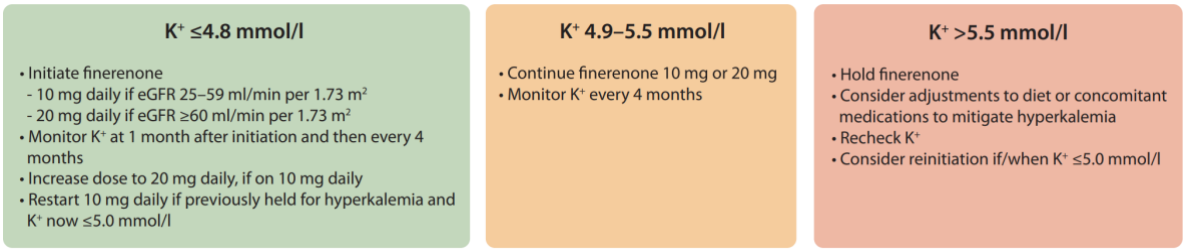


Figure 22. Serum potassium monitoring during treatment with a non-steroidal mineralocorticoid receptor antagonist (MRA) (finerenone). Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD). The United States Food and Drug Administration (FDA) has approved initiation of K^+ <5.0 mmol/l. This figure is guided by trial design and the FDA label and may be different in other countries. Serum creatinine/estimated glomerular filtration rate (eGFR) should be monitored concurrently with serum potassium.

3.8. Glucagon-like peptide receptor agonists (GLP-1 RA)

Recommendation 3.8.1: 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 3.8.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

3.9. Metabolic acidosis

Practice Point 3.9.1: In people with CKD, consider using dietary and/or pharmacological treatment to prevent severe acidosis (e.g., bicarbonate <16 mmol/l).

Practice Point 3.9.2: Monitor people with CKD to ensure correction of serum bicarbonate does not result in concentrations exceeding the upper limit of normal and does not adversely affect BP control, serum potassium, or fluid status.

3.10. Hyperkalemia in CKD

3.10.1. Awareness of factors impacting on potassium measurement

Practice Point 3.10.1.1: Be aware of the variability of potassium laboratory measurements as well as factors and mechanisms that may influence potassium measurement including diurnal variation, plasma versus serum samples, and the actions of medications.

3.10.2. Potassium exchange resins

Practice Point 3.10.2.1: Be aware of local availability or formulary restrictions with regards to the pharmacologic management of nonemergent hyperkalemia.

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

[No recommendations or practice points]

3.10.4. Managing hyperkalemia

[No recommendations or practice points]

3.10.5. Dietary considerations

Practice Point 3.10.5.1: For those people with CKD G3–G5 and emergent hyperkalemia, an individualized approach that includes dietary and pharmacologic interventions and takes into consideration associated comorbidities and quality of life is advised.

Assessment and education through a registered dietitian or accredited nutrition providers is advised.

Practice Point 3.10.5.2: 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.

3.11. Anemia

Please refer to the *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease* publications for specific recommendations, selection, and dosing of specific therapeutic agents, and research recommendations.[59]

3.12. CKD-Mineral Bone Disorder (CKD-MBD)

Please refer to the *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)* for specific recommendations, selection, dosing of specific therapeutic agents, and research recommendations.[16]

3.13. Hyperuricemia

Recommendation 3.13.1: We recommend people with CKD and symptomatic hyperuricemia should be offered uric acid-lowering intervention (1C).

Practice Point 3.13.1: 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 3.13.2: Xanthine oxidase inhibitors are preferred over uricosuric agents in people with CKD and symptomatic hyperuricemia.

Practice Point 3.13.3: 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 3.13.4: Nonpharmacological interventions which may help prevent gout include limiting alcohol, meats, and high-fructose corn syrup intake.

Recommendation 3.13.2: We suggest not using agents to lower serum uric acid in people with CKD and asymptomatic hyperuricemia to delay CKD progression (2D).

3.14. Cardiovascular disease (CVD) and additional specific interventions to modify risk

3.14.1 Lipid management

Recommendation 3.14.1.1: 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 3.14.1.2: 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 3.14.1.3: 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**
- **estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%**

Practice Point 3.14.1.1 Estimate 10-year cardiovascular risk using a validated risk tool.

Practice Point 3.14.1.2: 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 3.14.1.3: 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 3.14.1.4: Consider a plant-based "Mediterranean-style" diet in addition to lipid-modifying therapy to reduce cardiovascular risk.

3.14.2. Use of antiplatelet therapy

Recommendation 3.14.2.1: 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 3.14.2.1: Consider other antiplatelet therapy (e.g., $P2Y_{12}$ inhibitors) when there is aspirin intolerance.

3.14.3. Invasive versus intensive medical therapy for coronary artery disease

Recommendation 3.14.3.1: 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 3.14.3.1: Initial management with an intensive 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.

3.15. CKD and atrial fibrillation

Practice Point 3.15.1: Follow established strategies for the diagnosis and management of atrial fibrillation (Figure 35).

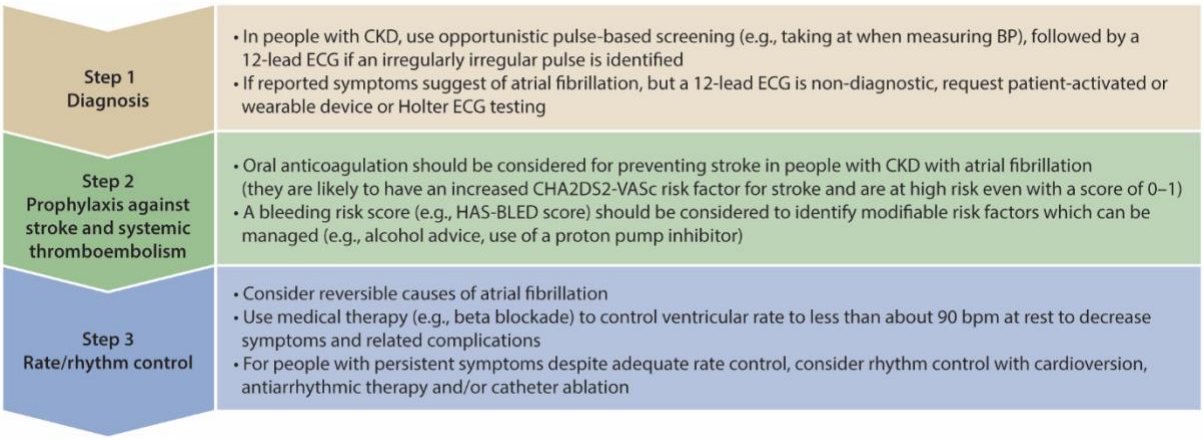


Figure 35. Strategies for the diagnosis and management of atrial fibrillation. *Consider dose adjustments necessary in people with CKD. †The following has been recommended as a standard package for diagnostic evaluation of new atrial fibrillation: (i) a 12-lead electrocardiogram (ECG) to establish the diagnosis, assess ventricular rate, and check for the presence of conduction defects, ischemia, or structural heart disease; (ii) laboratory testing for thyroid and kidney function, serum electrolytes, and full blood count; and (iii) transthoracic echocardiography to assess left ventricular size and function, left atrial size, for valvular disease, and right heart size and function. BP, blood pressure;

CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, and Sex category (female); CKD, chronic kidney disease; HAS-BLED, Hypertension, Abnormal liver/kidney function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly, Drug/alcohol usage.

Recommendation 3.15.1: 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 3.15.2: NOAC dose adjustment for GFR is required, with caution needed at CKD G4–G5.

Practice Point 3.15.3: Duration of NOAC discontinuation before elective procedures needs to consider procedural bleeding risk, NOAC prescribed, and level of GFR (Figure 39).

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local hemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	No official indication	No official indication	**≥36 h**	**≥48 h**
CrCl <15 mL/min	No official indication for use There is no need for bridging with LMWH/UFH			

Figure 39. Advice on when to discontinue non-vitamin K oral anticoagulants (NOACs) before procedures. Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk. Low risk is defned as a low frequency of bleeding and/or minor impact of a bleed. High risk defned as a high frequency of bleeding and/or important clinincal impact. Adapted from Heidbuchel *et al*.[60] [a]Many of these people may be on lower dose of dabigatran (110 mg twice per day [b.i.d]) or apixaban (2.5 mg b.i.d), or have to be on the lower dose of rivaroxaban (15 mg OD) or edoxaban (30 mg OD). Dabigatran 110 mg b.i.d has not been approved for use by the United States Food and Drug Administration. CrCl, creatinine clearance, LMWH, low-molecular weight heparin; UFH, unfractionated heparin. Reproduced from Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. European Heart Journal Table 3.[61]

CHAPTER 4. MEDICATION MANAGEMENT AND DRUG STEWARDSHIP IN CKD

4.1. 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, 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, dietary or herbal remedies that may be harmful for people with CKD.

Special considerations

Medications and pregnancy

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

4.2. Dose adjustments by level of eGFR

Practice Point 4.2.1: Consider eGFR 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 accuracy is required for dosing (e.g., due to narrow therapeutic or toxic range) and/or estimates may be unreliable, use 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 unadjusted 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, nonGFR determinants of the filtration markers, or volume of distribution are not in a steady state.

4.3. 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 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.

4.4. 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: In people with AKI or GFR <60 ml/min per 1.73 m^2 (CKD G3a–G5) undergoing elective investigation, the intravascular administration of radiocontrast

media for these patients can be managed in accordance with consensus statements from the radiology societies.

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.

CHAPTER 5. OPTIMAL MODELS OF CARE

5.1. Referral to specialist kidney care services

Practice Point 5.1.1: Refer adults with CKD to specialist kidney care services in the following circumstances (Figure 44):

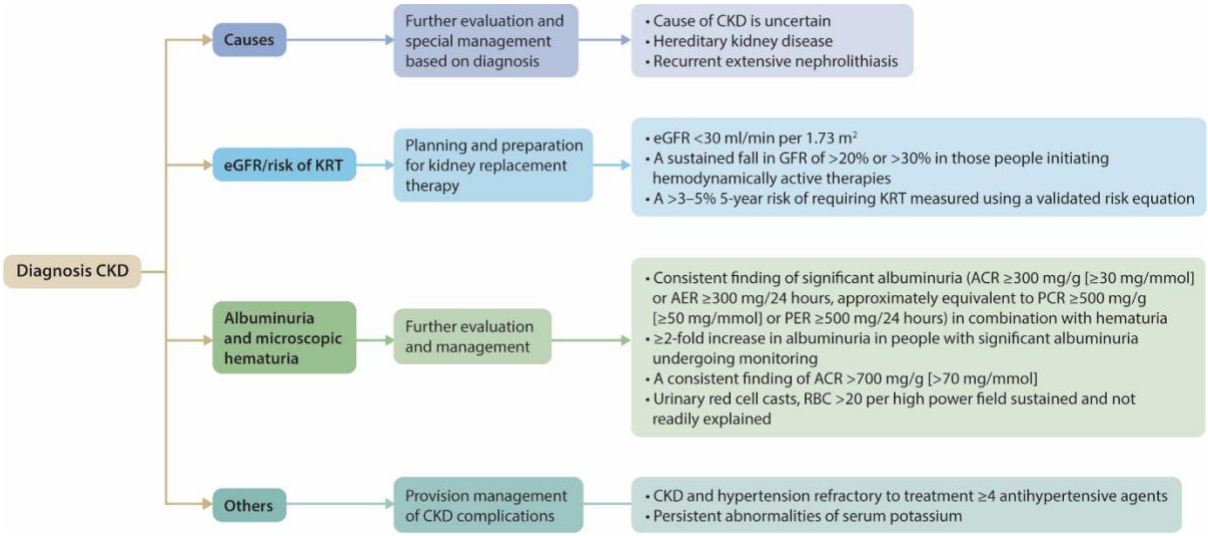


Figure 44. Circumstance for referral to specialist kidney care services and goals of the referral.
ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; PCR, protein-creatinine ratio; RBC, red blood cells

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 [20mg/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.**

5.2. Care of people with CKD G4–G5

5.2.1. Prevalence and severity of symptoms
[No recommendations or practice points]

5.2.2 Identification and assessment of symptoms
Practice Point 5.2.2.1: Ask people with CKD G4–G5 about uremic symptoms at each consultation (i.e., reduced appetite, nausea, level of fatigue/lethargy) using a standardized symptomatic assessment of uremic symptoms.

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 like 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, ideally under the supervision of accredited nutrition providers, for people with signs of malnutrition.

5.3. 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 carers/family 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 (Figure 51).

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 (Figure 51).

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

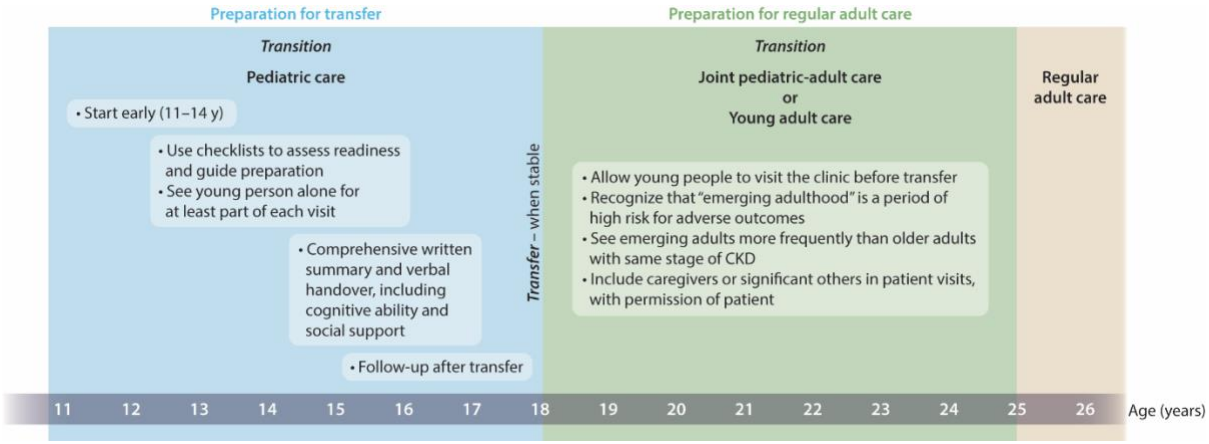


Figure 51. The process of transition from pediatric to adult care in chronic kidney disease (CKD).

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 risk of incomplete brain development.

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 (Figure 51).

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 (Figure 51).

5.4. Timing the initiation of dialysis

Practice Point 5.4.1: Initiate dialysis based on a composite assessment of person's symptoms, quality of life, patient 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 (Table 42). This often but not invariably occurs in the GFR range between 5 and 10 ml/min per 1.73 m^2.

Symptoms or signs attributable to kidney failure (e.g., neurological signs and symptoms attributable to uremia, pericarditis, anorexia, medically resistant acid-based or electrolyte abnormalities, intractable pruritus, serositis, acid-base or electrolyte abnormalities)
Inability to control volume status or blood pressure.
Progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.

Table 42. Indications for the initiation of dialysis.

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

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 eGFR 5–15 ml/min per 1.73 m^2.

5.5. 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: Enable 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.

CHAPTER 1. EVALUATION OF CKD

1.1. Detection and evaluation of CKD

Both decreased GFR and increased albuminuria or other markers of kidney damage are often silent and not apparent to the person at risk of CKD or the healthcare provider unless laboratory tests are performed. The cause of the decreased GFR or increased albuminuria may also not be apparent. In the decade since the publication of the previous *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*,[1] there have been substantial advances in treatment for CKD of all causes (Chapter 3), targeted therapies for specific causes of CKD (e.g., *KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases*[18]), as well as understanding of and methods to determine the etiology of CKD. All together these advances have the potential to slow and possibly prevent progression of kidney disease. Thus, in this section of Chapter 1, we emphasize first the importance of detection of CKD, then considerations for the optimal methods for staging of CKD, and how to establish chronicity and etiology.

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 either elevated albumin-to-creatinine ratio (ACR) or low estimated GFR (eGFR), repeat both urine albumin and eGFR tests to confirm presence of CKD.

Early detection of any chronic disease, including CKD, provides greater opportunities to reduce morbidity as treatments can be initiated earlier in the disease course. Because treatments for CKD provide benefits in reducing risk for both cardiovascular disease (CVD) and CKD progression, strategies that promote early detection of CKD should improve kidney and non-kidney related outcomes. Even if medical treatments are not available or indicated for an individual, there are recommended lifestyle changes that could be implemented following diagnosis of CKD (Chapter 3). Interviews with people who have CKD have provided evidence that many would alter their lifestyle if they received a diagnosis of CKD.[13] Knowledge of level of albuminuria and GFR also helps guide clinical decisions beyond initiating treatments specifically for CKD **(**Table 5). Each of these is considered in greater depth in subsequent chapters. Finally, since many kidney diseases have a familial component, diagnosis of the disease in one person may allow detection in other family members too. Thus, initial testing of blood and urine to detect CKD is important, with confirmatory testing if initial findings indicate the presence of abnormalities of creatinine/eGFR or albuminuria.

Clinical decisions	Current level		Change in level of GFR
	GFR	**Albuminuria**	
Diagnosis and staging	• Detection of CKD • Evaluation for kidney donation	• Detection of CKD	• Detection of AKI and AKD • Detection of CKD progression
Treatment	• Referral to nephrologists • Patient and family education about CKD and benefit of lifestyle changes • Monitor progression of GFR decline • Referral for kidney transplantation • Placement of dialysis access • Dosage and monitoring for medications cleared by the kidney • Determine safety of diagnostic tests or procedures • Eligibility for clinical trials	• Referral to nephrologists • Patient and family education about CKD and benefit of lifestyle changes • Monitor progression of GFR decline • Eligibility for clinical trials	• Treatment of AKI • Monitoring drug toxicity • Re-evaluate CKD treatment strategies
Risk assessment	• Risk of CKD complications • Risk for CKD progression • Risk of CVD • Risk for medication errors • Risk for perioperative complications • Risk for mortality • Fertility and risk of complications of pregnancy	• Risk for CKD progression • Risk for CVD • Risk for mortality • Fertility and risk of complications of pregnancy	• Risk for kidney failure • Risk for CVD, HF, mortality • Risk for adverse pregnancy outcome

Table 5. Use of glomerular filtration rate (GFR) and albuminuria. AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure

From a societal perspective, early identification of and intervention for CKD could have a positive impact on health disparities. In many countries, there is a higher incidence of CKD among people with lower socioeconomic status, and these people are more likely to progress to kidney failure and have less access to kidney replacement therapy (KRT; dialysis and transplantation).[62] A public health approach toward CKD detection and treatment could reduce inequities in the burden of kidney failure by slowing the rate of progression and the risk of CVD for everyone.[63]

The primary harm of early detection of CKD is that the new diagnosis may cause anxiety in some people, particularly if the testing is not discussed in advance of the results. Discussions around disease detection are common in the primary care setting, and shared decision-making is an established practice through which people may agree to the testing, confirm that they would like to be tested, and prepare for the range of possible results and their implications.[64-66] Another harm is increased burden and costs associated with physician visits or treatments which may not be balanced by savings from averting adverse outcomes.

CKD fits the World Health Organization (WHO) criteria for an early detection program.[67-69] Given that chronic disease detection and prevention frameworks have been deployed for other disease and risk factor conditions, in our view, CKD detection strategies should be implemented for high-risk people.

A framework has been developed for communities to align CKD detection and treatment strategies within their broader public health priorities to ensure that the goals of the intervention are achieved without compromising other valuable health initiatives.[22] Both the efficacy and the cost-effectiveness of CKD detection and treatment interventions will depend upon the specific strategies that are employed in the healthcare system. Therefore, future clinical trials should be evaluated within their unique context and may not generalize to all CKD detection efforts.

Most people with or at risk for CKD, healthcare providers, and policy makers would wish to identify CKD. Most people who are already receiving medical care would choose case-finding strategies to enable earlier risk stratification and treatment for previously undiagnosed CKD.[13, 70] Thus, the application of earlier treatment in order to delay CKD progression in people with CKD is of a higher priority than the lack of clinical trial evidence that case-finding strategies themselves improve outcomes.

This practice point promoting CKD detection efforts may have implications for health equity since CKD disproportionately affects people from minoritized populations and those who have lower socioeconomic status. The increasing availability and evidence supporting several treatments for CKD advocates for early disease detection. Given the asymptomatic progression of CKD, systematic testing of people with risk factors for CKD is the only method that would

detect CKD at early stages and allow initiation of appropriate treatments. CKD detection could reduce the proportion of people with CKD who will experience the morbidity of CKD G4-G5. Cost-effectiveness analyses performed in the new era of effective disease-modifying therapies, describe a more positive view of population wide screening.[23]

Figure 2 provides an algorithm for identification of people at risk for CKD, testing in those at risk, further testing in those identified as having CKD to confirm stages, subsequently allowing for treatment initiation. Primary care physicians or other medical specialists who care for people with risk factors for CKD, such as endocrinology, cardiology, or rheumatology, are ideal settings for an intervention that targets people with undetected CKD. Implementing an early detection intervention would be facilitated by integrated healthcare systems and the use of electronic health records. These structures would facilitate the linkage between risk stratification and treatment to have the desired effect of slowing the progression of CKD.

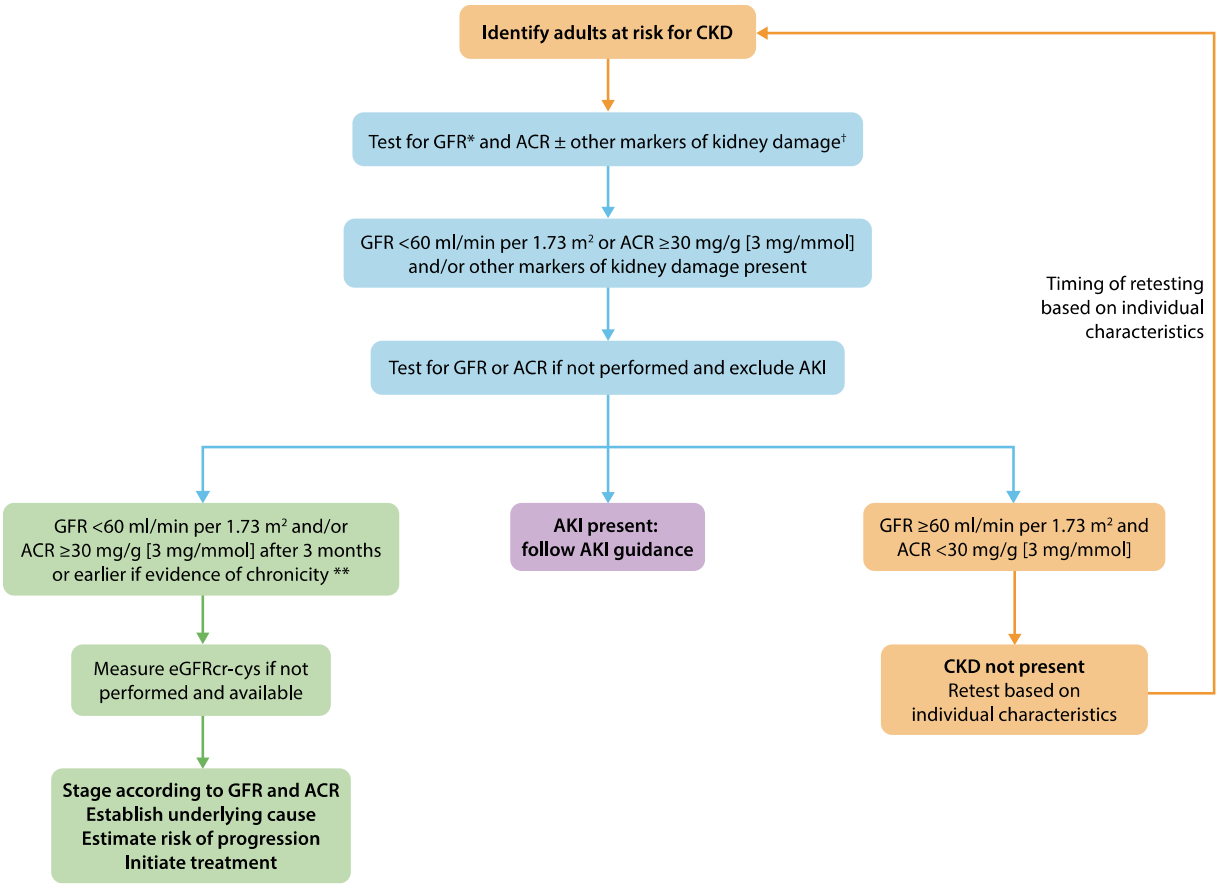


Figure 2. Screening algorithm for diagnosis and staging of chronic kidney disease (CKD). Risk factor conditions include hypertension; diabetes; cardiovascular disease; AKI/hospitalization history; FH kidney disease; obesity; other high-risk comorbidities (e.g., SLE, environmental exposures, nephrotoxic drugs, genetic factors, preeclampsia, low birth weight). *eGFR may be estimated using a creatinine-based estimating equation apart from certain conditions such as patients with large limb amputation, spinal cord

injury, neuromuscular disease, severe malnutrition, advanced heart failure, and liver disease where consideration should be given either to use of a combined creatinine-cystatin C estimated GFR, a cystatin C only estimated GFR, or urinary or plasma clearance measurement of GFR. †Markers of kidney damage other than albuminuria may also be used to diagnose CKD, but ACR and GFR should still be evaluated to determine stage and estimate risk of progression. Orange boxes indicate actions in people at risk for CKD and in whom testing should be performed. Blue boxes indicate testing steps. Green boxes indicate identification of CKD and its stages and initiation of treatment. Purple box indicates identification of AKI. Please also see the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*. ACR; albumin creatinine ratio; AKI; acute kidney injury; GFR, glomerular filtration rate; SLE; systemic lupus erythematosus. ** evidence of chronicity

The highest priority conditions for CKD detection are hypertension, diabetes, and CVD, including heart failure. A second important group are people with recent AKI, particularly multiple episodes of AKI, and those who have been "partially diagnosed" with CKD by either eGFR or albuminuria but cannot be fully staged. Other groups who might be considered for CKD testing are shown in Table 6. This list is not exhaustive and may be modified by local epidemiological considerations, though as per above, 2023 analyses suggest that population screening may in fact be cost-effective, obviating the need for "selecting" and addressing an ever changing list of "at risk" groups.

Domains	Example conditions
Common risk factors	Hypertension Diabetes Cardiovascular disease (including heart failure) Prior AKI
People who live in geographical areas with high prevalence of CKD	Areas with endemic CKDu Environmental exposures
Genitourinary disorders	Structural urinary tract disease Recurrent kidney calculi Gestational conditions
Multisystem diseases	Systemic lupus erythematosus Gout HIV Preeclampsia/eclampsia
Occupational exposures that promote CKD risk	Cadmium, lead, and mercury exposure Polycyclic hydrocarbons Pesticides
Family history	Kidney failure, regardless of identified genetic abnormality Hereditary kidney disease recognized to be associated with genetic abnormality (e.g., PKD, *APOL1* Disease, Alport syndrome)
Gestational conditions	Preterm birth Small gestational size Preeclampsia

Table 6. Risk factors for chronic kidney disease (CKD). AKI, acute kidney injury; CKDu, chronic kidney disease of undetermined origin; HIV, human immunodeficiency virus; PKD, polycystic kidney disease

Testing for CKD at all ages generates controversy. Those in older age groups experience the greatest burden of CKD and are also at the highest risk for cardiovascular complications. As with other detection programs like cancer detection, CKD detection efforts should be individualized based upon the person's goals of care and suitability for treatment.

There is known biological and analytical variability in SCr and in urine albumin or urine protein not related to their properties as markers of kidney disease. In people without risk factors for CKD, there is a low pretest probability for CKD. Thus, any unexpected results should be verified before diagnosing a person as having CKD. In people with risk factors for CKD, there is a higher probability that the person does have CKD even with an unexpected finding. Subsequent testing should be done to confirm the diagnosis and to complete the evaluation, as is required.

Special considerations

Pediatric considerations

People who are born preterm, especially if also small for gestational age, are at increased risk for CKD and kidney failure. This is largely related to decreased nephron number.[71-73]

1.1.2. Methods for staging of CKD

Recommendation 1.1.2.1: In adults at risk for CKD, we recommend that 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]); or if unavailable, use creatinine-based estimated glomerular filtration rate (eGFRcr) (1B).

For diagnosis and staging of CKD by GFR, this recommendation puts a high value on data suggesting that the most "accurate" method of estimating GFR is by using 2 biomarkers (cystatin C and creatinine) as each have limitations and benefits as filtration markers. As compared to mGFR, estimating equations using both creatinine and cystatin C afford greater accuracy in comparison to either filtration marker alone. The recommendation places a lower value on the resource utilization and cost associated with the assessment of eGFRcr-cys.

Key information

Balance of benefits and harms

In the CKD-PC collaboration, 720,736 people had measures of blood cystatin C in addition to having eGFRcr and ACR.[40] Replacing the assessment of eGFRcr with eGFRcr-cys in the matrix of GFR categories led to several changes in the risk distributions. Most notably, the group with an eGFR category 45–59 ml/min per 1.73 m^2 and ACR <10 mg/g were moved to higher risk for all 10 outcomes and this category was no longer labeled as being low-risk ("green") for any of the complications (Figure 5a-j). For the 8 outcomes that are not influenced by changes in creatinine (i.e., all except kidney failure and AKI), eGFRcr exhibited a J-shaped association such that risk increased with eGFR values >105 ml/min per 1.73 m^2 (Figure 6). In contrast, eGFRcr-cys demonstrated much more linear associations with each of these complications throughout its distribution. These data demonstrate that the combined eGFRcr-cys equation is superior for distinguishing GFR risk stages compared with eGFRcr.

Certainty of evidence

This recommendation is based on 2 broadly different types of data. Data comparing the accuracy (P_{30}) of equations from a combination of creatinine and cystatin C as filtration markers and creatinine and cystatin C alone; and data from the CKD-PC examining risk of outcome by GFR stage assessed by eGFRcr compared with eGFRcr-cys. As compared to equations based on creatinine and cystatin C alone, the equation using both creatinine and cystatin C comes closest to mGFR most consistently. The CKD-PC data was an individual-level data analysis of

27,503,140 participants from 114 global cohorts (eGFRcr) and 720,736 participants from 20 cohorts (eGFRcr-cys) and 9,067,753 participants from 114 cohorts (albuminuria) from 1980 to 2021 from around the world conveying a high degree of robustness in the association of CKD stage with a broad range of adverse outcomes. Based on the totality and consistency of the CKD-PC data, the overall certainty of the evidence was rated as moderate.

Values and preferences

This recommendation places a high value on the need for the most accurate assessment of GFR. The Work Group judged that many people at risk for CKD would prefer an accurate measurement when confirming the diagnosis of CKD and its staging. For this reason, the Work Group prioritized eGFRcr-cys over eGFRcr or eGFRcys for the most accurate measurement. The recommendation puts a low value on the availability and cost of an assessment of eGFRcr-cys suggesting that people at risk of CKD would opt for the more accurate assessment.

Resource use and costs

The costs and resource use associated with eGFRcr-cys are currently greater than those of eGFRcr; however, the need for an accurate measurement may offset these expenses. In addition, accurate diagnosis of CKD as early as possible may lead to lower resource utilization and healthcare spending than if diagnosed in later stages of CKD. For more information on the costs associated with cystatin C assessments, please refer to Section 1.2.2

Considerations for implementation

The biggest consideration for implementation is the availability of cystatin C measurement. For this reason, the recommendation includes the alternative for eGFRcr in such cases taking into consideration the limitations and drawbacks of creatinine-based measurements.

Rationale

The KDIGO CKD staging system based on the 2 dimensions, GFR and albuminuria, was created largely to reflect the association of outcomes of people with CKD, relative to the earlier staging systems based solely upon GFR stages. Assessment of GFR stage is ideally done using accurate assessment of GFR and ACR and is utilized to best capture the prognosis for people with CKD with regard to outcomes such as kidney failure, CVD, and mortality risk. There is now a large evidence base demonstrating that the use of eGFRcr-cys reclassifies a large proportion of the population into different GFR stages and the “new” stages better reflect their risk associations. For that reason, where available, cystatin C should be added to creatinine for the purpose of estimating GFR for CKD diagnosis and staging.

1.1.3. Evaluation of chronicity

Practice Point 1.1.3.1: Proof of chronicity (duration 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 as acute kidney injury (AKI) can present with eGFR and ACR abnormalities in the context of subtle clinical symptoms, and yet be due to an acute event/condition.

Practice Point 1.1.3.3: Consider initiation of treatments for CKD at initial identification if chronicity is deemed likely.

Kidney diseases may be acute or chronic.[1, 74] We explicitly but arbitrarily define duration of >3 months (>90 days) as delineating "chronic" kidney disease. The rationale for defining chronicity is to differentiate CKD from acute kidney diseases (such as acute glomerulonephritis [GN]), including AKI, which may require different timelines for initiation of treatments, different interventions and have different etiologies and outcomes.[75] The duration of kidney disease may be documented or inferred based on the clinical context. For example, a person with decreased GFR or kidney damage during an acute illness, without prior documentation of kidney disease, may be inferred to have AKI. Resolution over days to weeks would confirm the diagnosis of AKI from a variety of different causes. A person with similar findings in the absence of an acute illness may be inferred to have CKD, and if followed over time would be confirmed to have CKD. In both cases, repeat ascertainment of GFR and kidney damage is recommended for accurate diagnosis and staging. The timing of the evaluation depends on clinical judgment, with earlier evaluation for those suspected of having AKI and later evaluation for those suspected of having CKD.

For people with risk factors for CKD, delaying diagnosis for the sake of confirming chronicity over a period of >3 months can delay care. Many people may not recognize the importance of a repeat visit if treatment had not been initiated. Thus, initiating treatment both allows for earlier intervention and also indicates to people the importance of the disease.

Special considerations

Pediatric considerations

Newborns who clearly have kidney disease (e.g., severe congenital malformations of the kidney and urinary tract) do not need to wait 3 months to be designated to have CKD.

1.1.4. Evaluation of cause

Practice Point 1.1.4.1: Establish the etiology in all people identified as having CKD using clinical context, personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis (Figure 7).

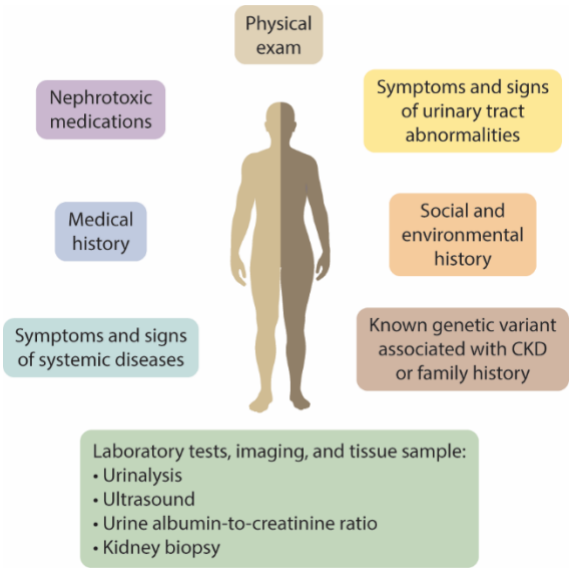


Figure 7. Evaluation of cause. CKD, chronic kidney disease

Practice Point 1.1.4.2: Use tests to establish a cause based on resources available (Table 7).

Test category	Examples	Comment or key references
Imaging	Ultrasound, intravenous urography, CT kidneys ureters bladder, nuclear medicine studies	Assess kidney structure (i.e., kidney shape, size, symmetry, and evidence of obstruction) for cystic disease, reflux disease. Evolving role of additional technologies (e.g., 3D ultrasound)
Kidney biopsy	Ultrasound guided percutaneous	Usually examined by light microscopy, immunofluorescence, and electron microscopy, and, in some situations, may include molecular diagnostics Used for exact diagnosis, planning treatment, assessing activity and chronicity of disease, and likelihood of treatment response; may also be used to assess genetic disease
Laboratory tests	PLA2R, ANCA, anti-glomerular basement membrane antibodies Serum free light chains, serum and urine protein electrophoresis/immunofixation	Refer to *KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases*[18] Increasing recognition of the role of light chains in kidney disease even in the absence of multiple myeloma (monoclonal gammopathy of renal significance [MGRS])[42]
Genetic testing	APOL1, COL4A, NPHS1, TRPC6	Evolving as a tool for diagnosis, increased utilization is expected. Recognition that genetic causes are more common and might be seen without classic family history.[43]

Table 7. Guidance for selection of additional tests for evaluation of cause. ANCA, antineutrophil cytoplasmic antibody; CT, computed tomography; PLA2R, M-type phospholipase A2 receptor

In evaluation of cause, healthcare providers should select specific diagnostic tests based on the pretest probability of a specific diagnosis informed by clinical presentation. Identification of cause confers benefit for targeting therapy to slow progression to kidney failure, understanding contributing factors, and prognosis. In addition, identification of cause can help people communicate information about a genetic or familial cause to relatives, improve understanding of their condition in the context of self-management, and improve health literacy. Genetic testing is emerging as a valuable component for evaluation of cause, but genetic findings may be costly, cause psychological distress without adequate support, lead to unnecessary medical tests and care, or possibly affect life insurance in some. Access to genetic counseling and medical genetics is important for psychosocial support and optimal use of genetic testing, respectively.[76] Absence of specific identification may also be a missed opportunity for targeted therapy.

The commonest causes of CKD are diabetes and hypertension both of which also are frequently found together with alternative primary causes of CKD. There is evidence of benefit partly from both the evidence underlying treatment of hypertension and diabetes to slow and or prevent progression of CKD, and from evidence of benefit from therapies targeted at specific causes of CKD (reviewed in *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD* and *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*[17, 19]). However, there are no studies examining the utility of establishing the underlying cause of kidney disease versus not in those people with identified CKD.

Most people with a new diagnosis of CKD and their healthcare providers would prefer to undertake evaluation for the underlying cause in order ensure the best possible care is provided. Although some people identified as having CKD may prefer not to undergo the (sometimes invasive) procedures to evaluate cause, establishing cause enables the most appropriate management strategy to be implemented.

Resources available for evaluation of cause will vary worldwide. People may not be able to pay for some diagnostic tests. Therefore, healthcare providers should tailor the evaluation of cause based on these resource constraints (e.g., urine protein reagent strip testing instead of ACR).

Education on the value of establishing a diagnosis of CKD is critical. This can be done through local, national, and international kidney societies and within health care training programs (Chapter 5). Additional resources may be required to support wider scale implementation of diagnostic tests, especially genetic testing, availability of biopsies, and the support required for implementation.

The starting point of the investigation of CKD is an assessment of eGFR and urine ACR. Identification of cause is often achieved by standard clinical methods (i.e., history, examination), knowledge of the causes of CKD and their manifestations, together with specialized investigations (Figure 7). Not all evaluations of cause are required in all people. Information from the clinical context and initial tests may lead to further evaluations (Table 7), which are likely to be conducted as part of specialized kidney care services and dependent on resources (Chapter 5).

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).

This recommendation places a high value on an acceptable safety profile of kidney biopsies when used to evaluate the cause of CKD and to plan appropriate treatment.

Key information

Balance of benefits and harms

The benefits of kidney biopsy in terms of diagnosis, prognosis, and planning appropriate treatment for both the person with CKD and healthcare providers are through improved understanding of the identified disease state and the extent of active and chronic lesions. The harms include the possibility of complications of the procedure (bleeding risk/ pain), the obtaining of a non-diagnostic or insufficient sample (wasted resource), and anxiety induced awaiting results.

The systematic review performed by the ERT identified 37 studies assessing the prognostic benefit and safety of kidney biopsy among people with CKD. Ten studies examined the diagnostic and/or prognostic benefit of kidney biopsy or influence of biopsy results on management decisions. The diagnostic findings were heterogeneous and variable which did not lend themselves to further synthesis. The rate of mortality after native kidney biopsy in people with suspected or diagnosed CKD was low. Across the 15 studies that reported on mortality after a native kidney biopsy, there were 3 reported deaths. The rate of perirenal hematoma across 14 studies was estimated to be 16% (95% confidence interval [CI]): 12%–22%. No studies reported on retroperitoneal hemorrhage (Supplementary Table S4).

Certainty of evidence

The overall certainty of evidence for kidney biopsy and outcomes of harms is very low (Supplemental Table S4). The critical outcomes, mortality and perirenal hematomas, were primarily assessed in observational studies without a comparison group. Because of the potential for confounding, the ERT considered the body of evidence to have serious study limitations. The certainty of the evidence for mortality was further downgraded because there were few events reported. The certainty of the evidence for perirenal hematomas was downgraded because there was significant statistical heterogeneity in the results across studies. The ERT did not identify any studies that reported on the critical outcome of retroperitoneal hemorrhage.

Values and preferences

The Work Group judged that many people with CKD would choose to undergo a kidney biopsy to establish the cause of their CKD more accurately and potentially offer prognostic information. Thus, this recommendation puts a high value on the specificity of a kidney biopsy

for the evaluation of cause as well as the very low certainty evidence demonstrating a low risk of complications associated with kidney biopsy. Because the potential that the information gleaned from the biopsy may not directly or immediately benefit the person, the Work Group judged that some people may prefer to decline a kidney biopsy. The decision to pursue biopsy should be a shared decision and be informed by probability of and utility of the information obtained on both diagnostic and prognostic fronts.

Resource use and costs

Resources available for evaluation of cause will vary worldwide and is dependent on the health care systems. People with CKD may not be able to pay for biopsy or afford the time away from work for the procedure. Resources in specific countries may not permit appropriate analysis of the obtained samples. Thus, healthcare providers' decisions to perform a kidney biopsy, in the presence of limited resources may therefore be influenced based on expected yield for that individual and the perceived value of the extra information gained.

Considerations for implementation

To optimize benefit and safety, a standardized approach for kidney biopsy with a vetted and standardized operating protocol designed for local implementation is warranted. Of note, most studies reported using ultrasound-guided biopsies, and older literature suggesting higher bleeding rates were done in the absence of guided biopsies, thus we might infer that there is a potential for higher rate of harms in "blind"/unguided biopsies.

Rationale

Kidney biopsy is an important part of the investigations for cause of CKD. It is often deferred because of the potential for harm or lack of recognition of potential utility. The evidence to support safety of biopsy is heterogeneous and therefore uncertain, but in the studies evaluated, appears to confer low risk of harm, supporting our suggestion that kidney biopsies should be considered when it is thought that they can provide information to identify cause, facilitate prognostication, and inform treatment strategies.

Special considerations

Pediatric considerations

Children and young people with kidney failure are more likely to have a genetic cause of their disease than adults. In some healthcare settings, genetic testing may be pursued first, obviating the need for kidney biopsy and the associated risks, which may be different in children than adults.

1.2. Evaluation of GFR

The kidney has many functions, including excretory, endocrine, and metabolic functions. GFR is one component of excretory function but is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other kidney functions decline in parallel with GFR in CKD.

In this section, we describe the overall approach for evaluation of GFR. As in the previous *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*,[1] the first method to evaluate GFR should be eGFRcr with subsequent supporting tests when required from either the more accurate eGFRcr-cys or measurement of GFR using urinary or plasma clearance of exogenous filtration markers. In contrast to the previous guideline, we emphasize the use of eGFRcr-cys based on accumulating evidence for its greater accuracy across populations and the use of mGFR given the known residual errors in all estimating equations. We also describe laboratory techniques and standards that satisfy the requirements for robust result reporting. We encourage healthcare providers to have a clear understanding of the value and limitations of both filtration markers and mGFR, the importance of standardization of assays for creatinine and cystatin C, and quality control procedures for exogenous markers. Finally, we describe currently available, validated estimating equations that can be used for reporting of GFR by clinical laboratories.

1.2.1. Other functions of kidneys 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.

The kidneys play several roles in the body, including metabolism and excretion of substances, volume and blood pressure regulation, erythropoietin production, and regulation of electrolytes, acid-base status, and mineral homeostasis. Glomerular filtration is one of many functions of the kidney. GFR is considered the best overall assessment of kidney functions as, in general, losses of these other functions correlate with loss of GFR. The term "kidney function" reflects the entirety of different and complex physiological functions of the kidney; thus, kidney function should not be a term used interchangeably with GFR.

Assessment of the overall functions of the kidney is a complex task. GFR is used as the primary tool to assess kidney function in practice. Loss of other kidney functions are known as complications of CKD and are addressed in Chapter 3. This section focuses on how GFR can be evaluated using both mGFR and eGFR.

Special considerations

Pediatric considerations

There are numerous kidney disorders in children that may present with tubular dysfunction (e.g., Bartter's, Dent Disease) rather than decreased GFR or albuminuria. These primarily result in polyuria and/or electrolyte disturbances and may or may not progress to reduced GFR or kidney failure. Thus, exclusive use of GFR in diagnosing CKD would not be of value in children, highlighting the importance of appreciating different markers linked to different kidney functions.

1.2.2. Evaluation of GFR: Guidance to physicians and other health care providers

We describe a framework for evaluation of GFR beginning with an initial test and followed by additional supportive tests (Figure 8, Tables 8 and 9).

Figure 8 depicts an algorithm for evaluation of GFR from initial test using eGFRcr, followed by decisions for when to perform supportive tests such as cystatin C or mGFR (Tables 8 and 9). Healthcare providers should consider both potential sources of error in eGFR as well as whether the clinical decision requires a highly accurate GFR when considering the need for additional tests. The level of accuracy that is needed for a clinical decision for use of potentially toxic medications, a medication with a narrow therapeutic window, or for other therapies with potential for adverse events may exceed the capability of any eGFR equation, and in such cases mGFR should be performed.

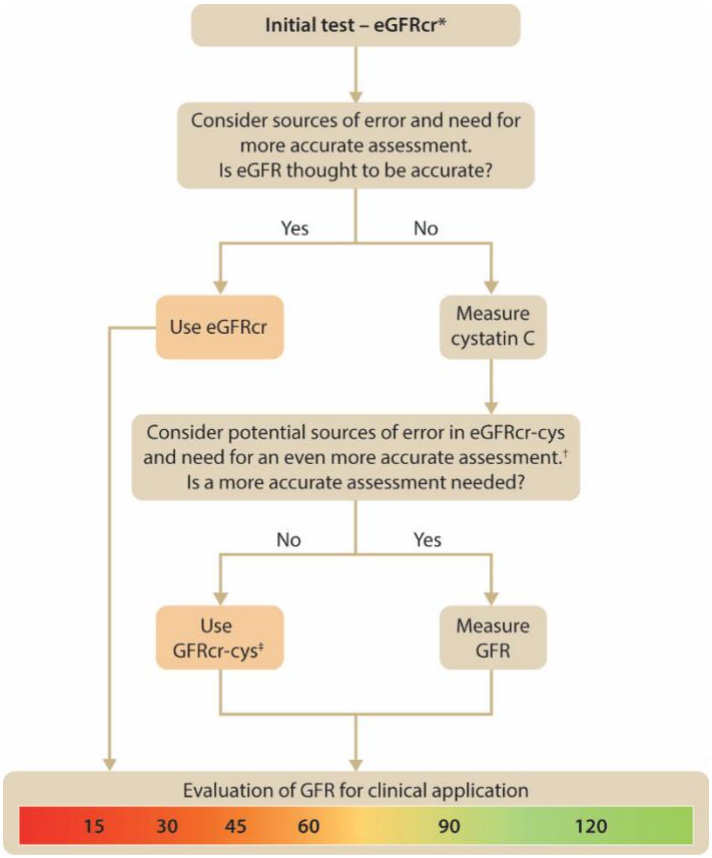


Figure 8. Approach to glomerular filtration rate (GFR) evaluation using initial and supportive tests.
The algorithm describes the approach to the evaluation of GFR. Our approach is to use initial and supportive testing to develop a final assessment of true GFR and to apply it in individual decision-making. The initial test for evaluation of GFR is creatinine-based estimated GFR (eGFRcr), which will be available in most people because creatinine is measured routinely as part of the basic metabolic panel. If eGFRcr is expected to be inaccurate, or if a more accurate assessment of GFR is needed for clinical decision-making, such as diagnosis or staging of CKD or drug dosing, then cystatin C should be measured, and creatinine and cystatin C-based estimated GFR (eGFRcr-cys) should be estimated. If eGFRcr-cys is expected to be inaccurate, or if an even more accurate assessment of GFR is needed for clinical decision-making, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. *Initial test may be estimated GFR by cystatin C (eGFRcys or eGFRcr-cys) in in otherwise healthy populations with changes in creatinine generation due to nonGFR determinants such as changes in muscle mass or creatinine secretion or extrarenal elimination due to use of specific medications. †Sources of error in eGFRcr-cys include very low muscle mass or very high levels of inflammation, high catabolic states, exogenous steroid use. ‡Consider eGFRcys rather than eGFRcr-cys in otherwise healthy populations with decreased creatinine generation due to reduced muscle mass or decreased creatinine secretion or extrarenal elimination due to use of specific medications

Practice Point 1.2.2.1: Use serum creatinine (SCr) and an estimating equation for initial assessment of GFR (Figure 8).

There are no RCTs to quantify the impact for use of less accurate methods versus more accurate methods of assessment of GFR. For most clinical circumstances, estimating GFR from SCr is appropriate for diagnosis, staging, and monitoring progression of CKD and observational data documented an increase in CKD recognition and referral to nephrologists shortly after the implementation of reporting of eGFR by clinical laboratories, especially for females and elderly people.[77-79] GFR is used in many routine and complex clinical decisions as an assessment of excretory kidney function (Table 5) to detect and stage acute kidney disease (AKD) and CKD, determine CKD progression, dose medications, determine appropriate use of diagnostic tests, and guide treatment decisions around KRT therapies. Equations are available that estimate GFR using SCr and adjusting for sex and age and professional societies throughout the world have recommended that GFR estimates should be used in association with SCr reporting. Sources of error in GFR estimation from SCr concentration include nonsteady state conditions, nonGFR determinants of SCr, measurement error at higher GFR, and interferences with the creatinine assays. GFR estimates are less precise at higher GFR levels than at lower levels and healthcare providers should remain aware of caveats for any estimating equation which may influence the accuracy in an individual person.

Most people with CKD and their healthcare providers would prefer the more accurate assessment of kidney function resulting from the use of GFR estimating equations compared to SCr alone. Minimal cost or resources issues are expected since creatinine is available in healthcare settings globally and evaluating GFR with the use of creatinine in the form of GFR estimating equations has been recommended for >20 years.

Estimated GFR from creatinine is widely used. Attention is required to implement and ensure the quality of eGFR reporting by clinical laboratories and ensure coordination with the electronic medical record, including those eGFR reports from point of care settings (Section 1.2.2)

GFR assessment method	Specific tests	Guidance for use and implementation
Estimated GFR	Creatinine (eGFRcr)	Most used method to assess GFR. In most cases, initial test for evaluation of GFR. Standardized assay required to decrease analytical variation
	Cystatin C (eGFRcr-cys, eGFRcys)	Used in selected circumstances as listed in Table 9 Standardized assay required to decrease analytical variation
mGFR	Gold standard. Urinary or plasma clearance of exogenous markers (e.g., iohexol, iothalamate, EDTA, DTPA)	Used in selected circumstances as listed in Table 9 Standard protocols for clearance methods and for standardized assay
Timed urine clearance	Creatinine	Highly prone to errors and recommended only when no other options for supportive tests for GFR evaluation; Performance under supervised conditions may decrease error
Nuclear medicine imaging	Imaging of the kidneys following injection of tracer cleared by the kidneys (e.g., 99mTc-DTPA scintigraphy	Highly prone to errors; not recommended

Table 8. Description of initial and supportive tests for evaluation of glomerular filtration rate (GFR).
DTPA, diethylenetriamine pentaacetate; EDTA, ethylenediaminetetraacetic acid; eGFRcr-cys, creatinine and cystatin C-based estimated GFR, eGFRcr, creatinine-based estimated GFR; eGFRcys, cystatin C-estimated GFR; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate

Recommendation 1.2.2.1: We recommend using eGFRcr-cys in clinical situations when eGFRcr is less accurate and GFR affects clinical decision-making (Table 9) (1C).

This recommendation places a high value on using estimates of GFR derived from a combination of creatinine and cystatin C in clinical situations where eGFRcr is an unreliable or inadequate assessment of GFR. There is consistent evidence that eGFRcr-cys provides more accurate estimates of mGFR than eGFRcr and eGFRcys in ambulatory people.

Key information

Balance of benefits and harms

Please see Practice Point 1.2.2.1 regarding the benefit of accurate assessment of GFR for clinical decision-making. In clinical practice, there may be situations where estimation of GFR from SCr alone may be a source of error, for example muscle wasting/loss, or where greater accuracy of GFR estimation is required for clinical decision-making (e.g., drug dosing). In most

of these situations estimating GFR using a combined creatinine and cystatin C equation provides the required degree of accuracy and obviates the need for expensive and time-consuming measurement of GFR using approved gold standard methodology. GFR estimating equations that incorporate both creatinine and cystatin C have particular benefit in terms of improved accuracy in relation to mGFR, compared to equivalent equations utilizing only one of these markers.[80-83]

In 2 large scale studies in pooled cohorts of general population cohorts or clinical populations in North America or Europe, the P_{30} using eGFRcr-cys are in the range of 90%,[80, 82-86] which is considered optimal.[1] Greater accuracy of eGFRcr-cys compared to eGFRcr or eGFRcys is also observed in studies evaluating GFR estimating equations compared to mGFR in other countries such as Brazil, Congo, Pakistan, Singapore, Japan and China,[87-95] with P_{30} estimated between 80% to 90%,[96] which is considered adequate for most decision-making.[1]

Harms include increased costs, as described below, and greater complexity in the interpretation of GFR with discrepant results between eGFRcr, eGFRcys and eGFRcr-cys. This in turn may lead to an increased number of nephrology consults, especially initially as healthcare providers may be unfamiliar with these new tests.

Certainty of evidence

The Work Group considered the overall certainty of the evidence to be moderate to high in ambulatory patients who were neither frail nor had acute or chronic illnesses, and low in other populations due to inconsistencies and imprecision in the studies currently available in the literature. Most of the studies used in the development and initial external validation of these equations were performed in ambulatory people who were neither frail nor had acute or chronic illnesses. There remains a paucity of studies examining the accuracy of eGFR in such populations.[53] Many studies that have been performed in such populations are small, increasing risk for analytical variability, and show inconsistent results among the studies even within the same disease. Some reports in populations with cancer, HIV, or obesity demonstrate greater accuracy for eGFRcr-cys than either eGFRcr or eGFRcys.[49-51, 97-99] Consistent with these findings, a large study of people living in Stockholm, Sweden referred for a mGFR test who had diagnoses for heart failure, liver failure, cancer, CVD, or diabetes found eGFRcr-cys to be the most accurate and least biased.[100] In other studies of sick or frail people, such as very advanced liver or heart failure or those admitted to the intensive care unit (ICU), all eGFR tests demonstrated very low levels of accuracy.[52, 57, 58, 101-103]

There are insufficient data to indicate the accuracy of eGFRcr, eGFRcys or eGFRcr-cys for many diseases. For example, in people with high cell turnover such as hematologic cancers, we expect that cystatin C would provide highly inaccurate estimates due to the increase in cystatin C because of cell turnover rather than decreased GFR disease.[104-108] However, there are no data to evaluate that hypothesis. Importantly, even for people from populations where

eGFRcr-cys has been demonstrated to be more accurate, healthcare providers should assess the potential sources of error in eGFR and the need for a highly accurate level of GFR. Among people who are frail or with multiple comorbid illnesses, eGFRcr-cys may be insufficiently accurate due to large contributions from nonGFR determinants of creatinine, cystatin C, or both markers.

Values and preferences

The Work Group judged that most people and most healthcare providers would want to use the most accurate assessment of GFR available to them and would, therefore, wish to estimate GFR from a combination of creatinine and cystatin C, when available. However, they would also balance additional costs associated with cystatin C against the potential benefits.

Differences between eGFRcr and eGFRcys may prompt recognition that both are estimates of GFR and both are associated with error, requiring interpretation as to the best estimate of GFR. In our view, this is desirable and uncertainty as to the level of GFR is an indication for nephrology referral.

Resource use and costs

Costs for higher frequency of cystatin C testing include one-time costs associated with initiation of the assay within a laboratory, which include building the information technology infrastructure and method verification studies, and continuous costs associated with maintaining the assay, which include reagents, daily quality control, requirements for calibration verification, and proficiency testing. Reagent costs are more expensive than creatinine but are lower compared to other commonly used biomarkers. If cystatin C is performed in an outside laboratory, other costs, as with any laboratory test, may ensue.

Considerations for implementation

We recognize that for these recommendations to be implemented, cystatin C needs to be widely available. Wherever possible, access to both creatinine and cystatin C measurements should be made available when evaluating GFR. Education for healthcare providers and people with CKD for optimal use and interpretation of these tests is required. See Section 1.2.3 for details regarding measurement of creatinine and cystatin C by clinical laboratories.

Rationale

We describe a framework for evaluation of GFR beginning with an initial test and followed by additional supportive tests (Figure 8, Table 8). Cystatin C is an alternative endogenous filtration marker that is now increasingly available. Its assay can be put on autoanalyzers and therefore its utilization could be increased with clinical demand. Creatinine and cystatin C-based eGFR (eGFRcr-cys) provides the most accurate estimate and is recommended as the primary supportive test for people in whom there are concerns about

eGFRcr accuracy (Table 9). However, there remain residual errors with some groups of people having a very high level of errors. In such people, we advocate using mGFR (Table 11).

Domain	Specific clinical condition	Cause of decreased accuracy	Comments on GFR evaluation
Body habitus and changes in muscle mass	Anorexia nervosa[44]	nonGFR determinants of SCr	eGFRcys may be appropriate if no comorbid illness other than reduction in muscle mass
	Extreme sport/exercise/body builder	nonGFR determinants of SCr	eGFRcys may be appropriate if increase in muscle mass is the only abnormality
	Above knee amputation[45]	nonGFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid conditions Suggest eGFRcr-cys in those with comorbid illness
	Spinal cord injury with paraplegia/paraparesis or quadriplegia/quadriparesis	nonGFR determinants of SCr	eGFRcys may be appropriate in those without other comorbid illness Suggest eGFRcr-cys in those with comorbid illness
	Class III obesity (BMI>40 kg/m^2)[†]	nonGFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate
Lifestyle	Smoking[46-48]	nonGFR determinants of SCys	Minimal data, suggest eGFRcr if no changes to nonGFR determinants of SCr or comorbid illness
Diet	Low protein diet	nonGFR determinants of SCr	Minimal data, suggest eGFRcys may be appropriate if no changes to nonGFR determinants of SCr or comorbid illness
	Keto-diets	nonGFR determinants of SCr	
	Vegetarian	nonGFR determinants of SCr	
	High protein diets and creatine supplements	nonGFR determinants of SCr	
Illness other than CKD	Malnutrition	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys because of coexistence of malnutrition and inflammation Suggest using mGFR for treatment decisions based on level of GFR
	Cancer[†49-51]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail people or in cancers with high cell turnover. Suggest using mGFR for treatment decisions based on level of GFR

	Heart failure[†52]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys highly inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Cirrhosis[†]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	eGFRcr-cys highly inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Catabolic consuming diseases[*]	Chronic illness, presumed impact on nonGFR determinants of SCr and SCys	Minimal data but eGFRcr-cys may be inaccurate. Suggest using eGFRcr-cys vs eGFRcr for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
	Muscle wasting diseases	nonGFR determinants of SCr	Suggest eGFRcys in those without other comorbid illness eGFRcr-cys in those with other comorbid illness
Medication effects	Steroids (anabolic, hormone)	nonGFR determinants of SCr. Effect on SCys not known	Physiological effect on SCys unknown, suggest eGFRcr-cys
	Decreases in tubular secretion	nonGFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness. Suggest using mGFR for treatment decisions based on level of GFR
	Broad spectrum antibiotics that decrease extrarenal elimination	nonGFR determinants of SCr	eGFRcys may be appropriate if medication affects only creatinine and no comorbid illness Suggest using mGFR for treatment decisions based on level of GFR

Table 9. Indications for measurement of cystatin C. eGFR, estimated glomerular filtration rate; eGFRcr-cys, creatinine and cystatin C-based estimated GFR, eGFRcr, creatinine-based estimated GFR; GFR, glomerular filtration rate; SCr, serum creatinine; SCys, serum cystatin C. [*]Catabolic consuming disease may include tuberculosis (TB), acquired immune deficiency syndrome (AIDS), hematologic malignancies, severe skin diseases. There is no data with measured glomerular filtration rate (mGFR) to evaluate this directly. [†]Data summarized in Adingwupu et al.[53]

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 (Table 10).

Given the benefit of accurate assessment of GFR for clinical decision-making, there is a need to appreciate the value and circumstances in which directly measured GFR (mGFR) is required. The greatest benefit of mGFR is that it is independent of all nonGFR determinants, in contrast to eGFR. GFR is measured using exogenous filtration markers and urinary or plasma clearance. Accuracy of mGFR can be determined from variability with repeated measures. Time-to-time variability is the method used to assess error.

Estimated GFR by SCr and/or cystatin C	Measured GFR
Inexpensive and easy to implement	More expensive, more time-consuming, and invasive
Widely available and may also be used at point of care, easily repeatable	Only available in certain centers Microsampling tests by fingerpick enables point-of-care testing
Not sufficiently accurate and precise for all clinical situations	Accurate for GFR in all situations and across the GFR range
Lags behind changes in GFR	Able to identify early changes in GFR
Subject to nonGFR determinant confounding	Not subject to nonGFR determinants

Table 10. Comparison of estimated glomerular filtration rate (GFR) and measured GFR. SCr, serum creatinine

One systematic review summarizing the available data comparing current GFR measurement methods to each other and to the classic gold standard of inulin urinary clearance recommended use of iothalamate, iohexol, ethylenediaminetetraacetic acid (EDTA), and diethylenetriamine pentaacetate (DTPA) as exogenous markers of choice.[108] A subsequent study recommended against plasma 99mTc-DTPA, especially when clearances are performed over 2–4 hours.[109] Several studies demonstrate that the method by which the clearance of exogenous markers is measured may impact accuracy. For example, for people with lower GFR an extended time period of blood sampling is required and in people with extensive oedema using plasma clearance generates error.[110] Finally, it is well-recognized that assessing GFR using imaging of nuclear tracers is less accurate than eGFR, and we do not recommend it as a method to measure GFR.[111]

Evaluation of time-to-time variability of plasma clearance of iohexol and eGFR found a within subject biological coefficient of variation (CV) for mGFR of 6.7% (95% CI: 5.6–8.2), whereas CV for eGFRcr, eGFRcys and eGFRcr-cys were approximately 5.0%.[112] Other studies

have observed CV for this same mGFR method ranging approximately 5%–10%.[112-116] There is less data for other methods, for urinary clearance of iothalamate, estimated CV were 6.3% and 16.6% across two studies.[115, 116]

The Work Group judged that there will be some clinical situations where estimating GFR from both creatinine and cystatin C will be insufficiently reliable and increased precision, the greatest benefit and least harm will be achieved by measuring GFR with the appropriate standardized methods.

Costs for mGFR are variable and harder to quantify. The infrastructure required is greater, as testing requires both patient and personnel time for inserting a peripheral intravenous catheter, administering the exogenous marker, collecting serial blood specimens over several hours (depending on the protocol), and the associated materials for the collection and measuring blood levels by high-performance liquid chromatography or mass spectrometry.

All nephrologists ideally should therefore have access to at least one method to measure GFR using plasma or urinary clearance of exogenous markers. To ensure highly accurate measurements, these clearance methods should be performed using standard operating procedures. External quality assessment (EQA) should be used for assays of the exogenous markers. Special considerations in clearance methods are required for some populations to obtain a high level of accuracy (e.g., later sampling time for people with low GFR or urinary, instead of plasma clearance for edematous people). GFR centers under the direction of a nephrologist champion or laboratory director, analogous to cardiac imaging, are likely to help both increase utilization and ensure high quality results. There will be additional requirements for storage, administration, and disposal if radionuclide methodologies are adopted. National kidney societies can work with payers to support reimbursement for mGFR procedures. The European Kidney Function Consortium (EKFC) together with the European Federation of Clinical Chemistry and Laboratory Medicine is currently harmonizing mGFR protocols to deliver standardized operating procedures for GFR measurements in the near future.

Decisions to measure GFR should be made by both nephrologists and other physicians using the framework suggested in Figure 8. Physicians should determine how accurate the GFR needs to be for a specific clinical decision. If greater accuracy is needed than can be achieved using eGFR, mGFR is recommended. Greater accuracy may be required due to inaccuracy of eGFR in the individual person due to presence of non GFR determinants or due to the requirement of the clinical setting. Table 11 lists indications for when one might consider mGFR as opposed to eGFRcr-cys.

We describe a framework for evaluation of GFR beginning with an initial test and followed by additional supportive tests (Figure 8, Table 8). Measured GFR is recommended

when there are concerns about the accuracy of eGFRcr-cys (Table 9) and where an accurate level of GFR is required for optimal decision-making, as described in Table 11).

Clinical conditions in which eGFRcr-cys is inaccurate or uncertain due to potential nonGFR determinants of creatinine and cystatin C. This may include catabolic states, such as serious infections or inflammatory states; high cell turnover as in come cancer; advanced cirrhosis or heart failure; use of high dose steroids; or the very frail. See Figure 9 for approach to individual decision-making.
Clinical settings in which greater accuracy is needed than is achieved with eGFRcr-cys. For example, decisions about simultaneous kidney transplant at the time of other solid organ transplant, kidney donor candidacy, drug dosing if narrow therapeutic index or serious toxicity (e.g., chemotherapies that are cleaned by the kidney).

Table 11. Indications for measured glomerular filtration rate. eGFRcr-cys, estimated GFR by creatinine and cystatin C

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.

All studies evaluating performance of eGFR compared to mGFR observe error in any GFR estimate. Even in populations where there is a high accuracy (i.e., P_{30} of 90%), 10% of the population would have errors ≥30% relative to mGFR. Within these studies, error rates are likely to be higher in some subgroups and lower in others. A critical component of the recommended approach to evaluation of GFR (Figure 8) is that physicians have a clear understanding of the value and limitations of eGFR and mGFR, which defines when a person requires one or another supportive test.

The source of error in eGFR may be related to errors in eGFR or in mGFR (Figure 9). The most important sources of error are nonGFR determinants of either creatinine or cystatin C. The nonGFR determinants of creatinine include generation by diet and muscle mass, tubular secretion, and extrarenal elimination.[47, 117] The nonGFR determinants of cystatin C are less well-understood but thought to be higher adiposity, smoking, hypo- and hyperthyroidism, glucocorticoid excess, and chronic inflammation (as indicated by insulin resistance, higher levels of C-reactive protein and tumor necrosis factor, or lower levels of serum albumin).[46, 47, 118-127]

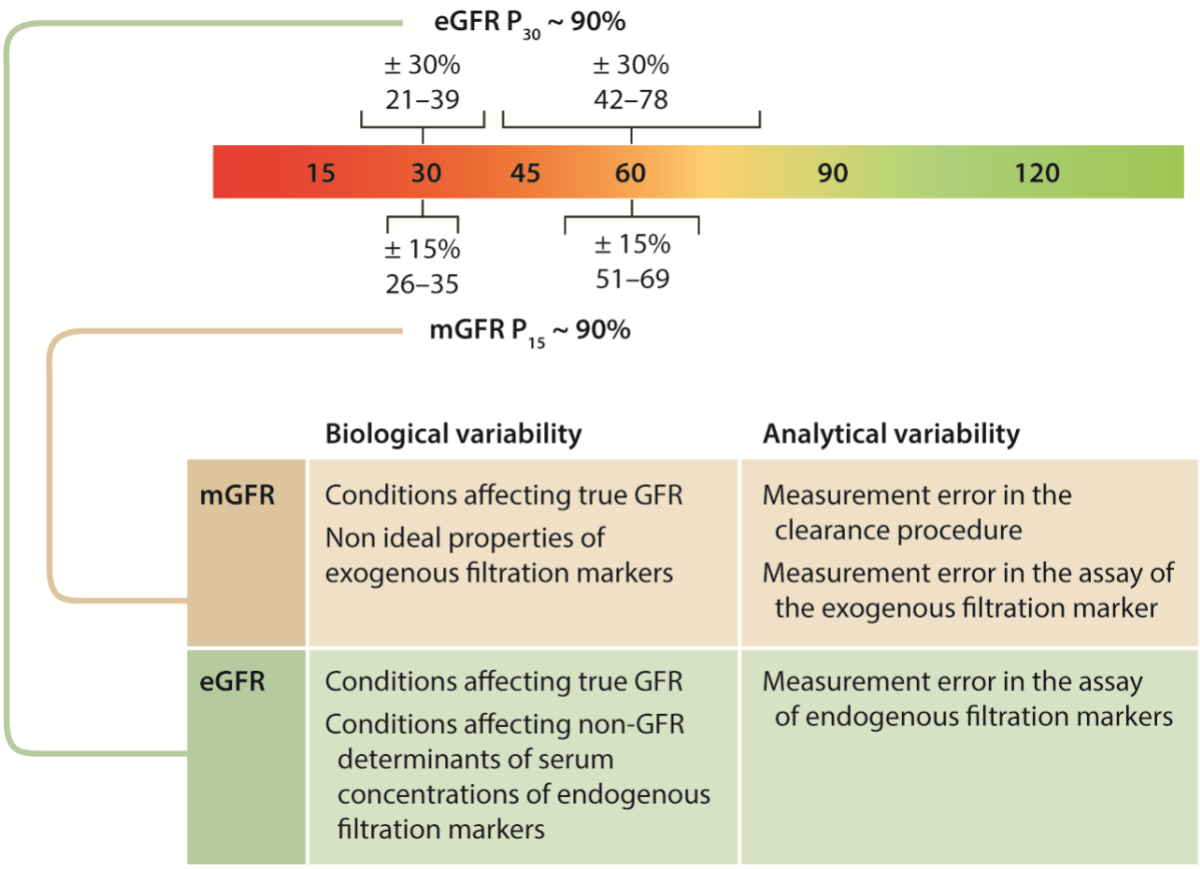


Figure 9. Sources and magnitude of error around measured (mGFR) and estimated glomerular filtration rate (eGFR). It is important to determine how accurate the assessment of glomerular filtration rate (GFR) needs to be for clinical decision-making. P_{30} for eGFR refers to the percent of eGFR that are within 30% of mGFR. If accuracy within 30% is acceptable (P_{30} >80%) or optimal (P_{30} >90%), eGFR may be sufficient, provided there are not large deviations in nonGFR determinants of creatinine or cystatin C. If greater accuracy is needed, mGFR is advised. The accuracy for mGFR are based on time-to-time variability. P_{15} for mGFR refers to the percent of one mGFR that was within 15% of the second. At a GFR of 60 ml/min per 1.73 m^2, 30% accuracy for eGFR corresponds to 42–78 ml/min per 1.73 m^2 and 15% accuracy for mGFR corresponds to 51–69 ml/min per 1.73 m^2. At a GFR of 30 ml/min per 1.73 m^2, 30% accuracy for eGFR corresponds to 21–39 ml/min per 1.73 m^2 and 15% accuracy for mGFR corresponds to 26–35 ml/min per 1.73 m^2. NonGFR determinants of endogenous filtration markers include generation, tubular handling and extrarenal elimination. Non ideal properties of exogenous filtration markers include tabular handling and extrarenal elimination.

Measured GFR also differs from the true physiological GFR which itself cannot be directly measured. Errors may be related to analytical errors in the assay or the clearance procedure. For example, overestimation of GFR is seen if late samples are not taken for people with low GFR.[109, 110] Urinary clearances are preferred to plasma clearance methods in people with extensive third spacing of fluid. As described earlier, several reports have documented CVs of 5% and 10%.[112-116] In the absence of changes related to disease progression, change in mGFR from time to time may occur due to preanalytical (e.g., patient preparation, time of day),

analytical (laboratory measurement variability) and biological (changes in true physiological GFR) variability. This does not detract from the advantage of mGFR as being free from nonGFR determinants. It is important for nephrologists to appreciate and understand these errors and nuances to appropriately order the right tests in specific circumstances.

Practice Point 1.2.2.4: Wait at least 12 hours before measurement of SCr, following meat or fish intake.

Most studies measuring GFR for clinical or research purposes are performed in the morning following a period of fasting or moderate protein intake. Ideally, optimal application of eGFR would simulate these conditions. Several studies have documented the impact of a cooked meat or fish meal on creatinine concentrations.[128] For example, one study demonstrates increase in SCr of approximately 20 µmol/l (0.23 mg/dl) which in the study population was equivalent to decrease in eGFR of approximately 20 ml/min per 1.73 m^2. Maximum post-prandial effects were reached in some subjects by 2 hours and others by 4 hours.

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

When evaluating change in eGFR over time, the question is whether the true GFR is changing. However as described above, there are several other potential causes for a change in observed eGFR, other than AKI, such as changes in nonGFR determinants of the filtration markers or analytical errors in the assays. Healthcare providers should consider whether there has been a change in nonGFR determinants (e.g., a recent meat meal now or at the first measurement or change in muscle mass or extreme activity) The impact of the combined effect of analytical and biological variation on eGFR is determining progression is discussed in Chapter 2. When evaluating change in GFR using mGFR, the combined effect of changes in biological and analytical variation should be considered as part of the interpretation of the results (Figure 9).[112]

Practice Point 1.2.2.6: Cystatin C-based estimated glomerular filtration rate (eGFRcys) may be indicated in some specific circumstances.

The combination of eGFRcr and eGFRcys together is more accurate than eGFRcr or eGFRcys alone.[80, 84] The greater accuracy is due to the fact that the nonGFR determinants for each marker are different, and therefore using both leads to convergence on the estimate of GFR and minimizes the effect of either marker.[129]

In individuals where nonGFR determinants of creatinine or cystatin C are substantially greater than for the other marker, then eGFRcr-cys would not provide the more accurate estimate. This imbalance is more likely to occur for creatinine, given its association with diet and

muscle mass which can vary greatly across various people. In such cases, it would be reasonable to use eGFRcys

The nonGFR determinants for cystatin C are less well studied, and it is erroneous to assume that eGFRcys provides the more accurate estimate in all circumstances. We, therefore, advise limiting this strategy to selected clinical settings where people are otherwise healthy with known changes in nonGFR determinants of creatinine. For example, in 1 study which compared eGFRcr and eGFRcys before and after amputation in otherwise healthy military veterans, there was a sizable change in eGFRcr as would be expected with the loss of a limb and loss of mobility, but no change in eGFRcys.[45] In another study of people with anorexia, serum levels of cystatin C were more strongly correlated with mGFR than were levels of SCr, but this has not been further evaluated using eGFR and standardized assays.[44] Other situations may be where there are medications which inhibit tubular secretion of creatinine, although there are no studies to provide evidence to drive guidance.

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.

For people who have simultaneous SCr and cystatin C values, the agreement or discrepancy between eGFRcr and eGFRcys may help to guide further actions. Several studies have demonstrated that 25%–30% of people have discordance between eGFRcr and eGFRcys as large as or larger than 15 ml/min per 1.73 m^2 or ≥20%.[100, 130, 131] One study demonstrated that factors associated with higher values for eGFRcr compared to eGFRcys included older age, female sex, non-Black race, higher eGFR, higher BMI, weight loss, and current smoking.[132] Two recent studies demonstrate that when there is concordance between eGFRcr and eGFRcys, there is high and similar accuracy for eGFRcr, eGFRcys and eGFRcr-cys with estimated P_{30} of 87%–91%.[100, 130, 131] In contrast, when there is discordance, eGFRcr-cys is more accurate than either eGFRcr or eGFRcys. This suggests that when eGFRcr and eGFRcys are discordant it is reasonable to continue to measure cystatin C serially in addition to creatinine in those settings where GFR will affect clinical decisions. It is also reasonable to consider performing/conducting mGFR when using medications with narrow therapeutic index or high toxicity or to inform critical treatment decisions (Chapter 4).

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

Measured GFR is not available everywhere. In these settings, it might be reasonable to consider measured urinary creatinine clearance (CrCl). It is widely available and therefore commonly used but is highly prone to error due to under- or overcollection. A systematic review

of GFR methods observed a mean bias of 25% across 23 studies, and as such did not find this method to reach sufficient accuracy.[108] The errors occur in both directions and thus do not appear solely due to the presence of tubular secretion of creatinine, which would be expected to overestimate mGFR. For example, in the pilot study for the African American Study of Kidney Disease (AASK), 25% of participants had a 24-hour measured CrCl that was at least 18% lower than the mGFR, and another 25% had measured CrCl at least 23% greater than the GFR. Of note, measured CrCl had substantially better correlation with mGFR when it was measured during an mGFR procedure;[133] therefore, if measured CrCl is to be performed, then it should ideally be supervised given the high risk of inaccuracy with urine collection.

Special considerations

Sex and gender considerations

It is unclear how best to estimate GFR in people who are transgender, gender-diverse, or non-binary where a person's gender identity is different from their sex assigned at birth. Gender-affirming testosterone therapy is associated with an increase in SCr concentration,[134] with less certainty for the impact of estrogen. The impact of gender-affirming hormone therapy, if any, on true GFR is unknown. In keeping with guidance from the American Association of Clinical Chemistry and the National Kidney Foundation,[135] evaluation of eGFR should use a shared decision-making approach with the person with CKD, taking into account muscle mass, sex hormone milieu, sex assigned at birth, and gender identity. We also note that the new EKFC cystatin equation does not include a variable for sex and the differences between eGFR for males and females using the CKD-EPIcys equation are much smaller compared to difference for males and females using the CKD-EPIcr equation, thus use of eGFRcys may avoid or minimize challenges with the use of eGFRcr.

Pediatric considerations

There are currently insufficient externally validated data to assess if combining creatinine and cystatin improves the performance of pediatric eGFR equations. Internal analysis of the Chronic Kidney Disease in Children (CKiD) cohort revealed averaging the eGFRcr and eGFRcys reduced mean bias in people who are Black, White, and Other race. Likewise, averaging eGFRs derived from the equations improved accuracy to 89%–91% (as assessed by P_{30}) across race groups. This has not been externally validated.[136]

1.2.3. Evaluation of GFR: Clinical laboratories

Practice Point 1.2.3.1: Implement the laboratory standards of care outlined in Table 12 to ensure accuracy and reliability when assessing GFR using creatinine and cystatin C.

• Report eGFR in addition to the serum concentrations of filtration markers using valid equations.
• Report eGFR rounded to the nearest whole number and relative to a body surface area (BSA) of 1.73 m^2 in adults using the units ml/min per 1.73 m^2.
• Reported eGFR levels <60 ml/min per 1.73 m^2 should be flagged as being low.
• When reporting levels of filtration markers, report (i) SCr concentration rounded to the nearest whole number when expressed as standard international units (µmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl). (ii) serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/l).
• Measure filtration markers using a specific, precise (coefficient of variation [CV] <2.3% for creatinine and <2.0% for cystatin C) assay with calibration traceable to the international standard reference materials and desirable bias (<3.7% for creatinine, <3.2% for cystatin C) compared to reference methodology (or appropriate international standard reference method group target in external quality assessment [EQA] for cystatin C).
• Use an enzymatic method to assay creatinine.
• Process blood for creatinine by the laboratory within 12 hours of venipuncture.
• When cystatin C is measured, measure creatinine on the same sample to enable calculation of eGFRcr-cys

Table 12. Implementation standards to ensure accuracy and reliability of glomerular filtration rate assessments using creatinine and cystatin C. eGFR, estimated glomerular filtration rate; eGFRcr-cys, estimated glomerular filtration rate based on creatinine and cystatin C; SCr, serum creatinine

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.

Consistency, standardization, and comparability of laboratory measures of creatinine and cystatin C, the reporting of results and of GFR estimates and the flagging of reported results where indicated are of paramount importance. The assays used should have the required specificity for the analyte and calibration of assays is essential to interpretation of kidney function measures. Results should be traceable to reference materials and methods listed on the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database.

Estimation of GFR improves identification of CKD. Adoption of the laboratory standards described here will ensure that healthcare providers receive eGFR reports in a consistent style and with assurance regarding the accuracy and reliability of the result. Flagging decreased values

for eGFR can alert healthcare providers to the possibility of kidney disease and may indicate the need for additional evaluation or adjustment of doses of medications that are excreted by the kidney.

Globally, most creatinine measurements are undertaken using a colorimetric method (Jaffe). This method also reacts with a variety of substances that are not creatinine (so-called "non-creatinine chromogens", e.g., glucose, acetoacetate), typically comprising some 20% of the measured substance reported as creatinine in adults at physiological creatinine concentrations. Enzymatic assays are available which are more specific for creatinine and less susceptible to chemical and chromogenic (e.g., icterus, hemolysis) interferences. Although enzymatic methods are not totally immune to the interferences affecting the Jaffe method and may be susceptible to other interferences specific to the enzymatic approach, in the majority of people, use of an enzymatic method will reduce the possibility of interference (Table 13). It is likely that cystatin C measurements will be less susceptible to chemical and spectral interferences affecting creatinine assays, but inevitably interferences will surface with more extensive clinical experience. For example, those due to circulating antibodies that are seen with other immunoassays.[137-139]

Following venipuncture, in unseparated samples there is a gradual increase in measured SCr over time when the Jaffe assay is used. This effect is not seen when enzymatic assays are used.[140] We therefore advise that serum should be removed from the red blood cells within 12 hours of venipuncture when the Jaffe assay is being used.

As described in Section 1.2, eGFR is an imperfect estimate of mGFR. At best 90% of eGFR will fall within 30% of mGFR. As shown in Figure 9, one of the sources of error is analytical variability in measurement of the filtration markers. Optimization of laboratory measurements of creatinine and cystatin C can help to reduce the uncertainty inherent in GFR estimation. The components of measurement error which laboratories must address are accuracy (trueness of the result), imprecision (analytical variability of the result, commonly expressed as a coefficient of variation [CV]) and specificity (reduction of interferences in the measurement). The availability of international reference standards for both creatinine[141] and cystatin C[142] and demonstration that the laboratory results have minimal bias compared to these help to ensure the accuracy of results. Imprecision targets are commonly based on the known biological variability of biomarkers (https://biologicalvariation.eu/). Analytical variability that is less than half the within-person biological variability is generally considered desirable.[143] The target CVs proposed here for creatinine and cystatin C should be achievable by automated laboratory methods. Achieving the target precision and bias goals proposed will ensure that laboratory error contributes to a less than 10% increase in root mean square error when estimating GFR.[144]

Most people with CKD, healthcare providers and policy makers would want laboratories to implement calibrated assays for creatinine and cystatin C that comply with international standards and use reagents for analysis that conform to internationally approved reference materials. Compliance with the recommended standards would ensure confidence in the results and in clinical decisions and any changes in management and treatment made as a consequence.

Globally most GFR estimates are currently produced using creatinine results generated by Jaffe assays, which are relatively inexpensive. Use of more specific enzymatic creatinine assays can improve estimation of GFR. However, enzymatic creatinine assays are more expensive than Jaffe assays. Use of cystatin C in combined creatinine-cystatin C GFR equations can also further improve GFR estimation, but cystatin C measurement adds significantly to the cost. Although the per-patient cost increase of enzymatic creatinine and cystatin C measurement is relatively small, implementation of these more expensive approaches have significant cost implications across entire healthcare systems.

Implementation considerations include the following:

Creatinine: Resource limitations that may restrict access to enzymatic creatinine should not be seen as a barrier to implementation of a GFR reporting program based on Jaffe creatinine measurement.

Cystatin C: Cystatin C can be available either within each local laboratory or alternatively as a referred test in centralized laboratories. A range of commercially available routine clinical biochemistry analyzers from a variety of manufacturers can support cystatin C assays and will allow turnaround time for results to be as rapid as that for routine electrolytes and creatinine where provided locally. Timeliness will affect utilization (i.e., if results are available on the same day), then the test is more likely to be useful for routine or urgent decisions and this may increase the pressure on laboratories to provide this test locally.

Estimated GFR: Implementation and modification (e.g., a change in equation) of GFR estimation requires close communication between the laboratory and a range of clinical users, including primary and secondary care healthcare providers, pharmacists, dieticians, and people with CKD.[145] Laboratories should only use GFR estimating equations that have been sufficiently validated in the population to which they are being applied and that are appropriate for the creatinine and cystatin C assays in use (Section 1.2.4).[145] They should also ensure that their end-to-end reporting processes, including calculations embedded within the laboratory information system, are subject to regular external quality assessment. Laboratory reports for computed values should indicate the filtration marker (i.e., eGFRcr, eGFRcys and eGFRcr-cys). Documentation should indicate which equation was used.

To aid clarity in reporting across and within healthcare systems, and to provide guidance regarding the number of meaningful digits in a result, a standardized approach in relation to reporting units of GFR, creatinine, and cystatin C should be implemented. Input age may be rounded to whole numbers or as a fractional year because the influence on eGFR is small. To adjust GFR for differences in body size, mGFR is commonly adjusted for BSA, with a population average BSA value of 1.73 m^2 being used. In practice, eGFR values derived using most equations are already adjusted for BSA, because BSA was taken into account when the equations were originally developed using regression modelling against BSA-adjusted mGFR.

Estimated GFR is mostly computed using the information recorded in the sex variable in electronic medical records. Some electronic medical records include legal sex, sex assigned at birth and gender identity, whereas others include only one variable. In some cases, this variable may be missing, or reported as non-binary. In these cases, eGFR values cannot be computed and will be displayed as a missing value. Laboratories should add a comment directing healthcare providers and people with CKD to online calculators to facilitate a shared decision-making approach to the person with CKD. The comment may also include a suggestion to use cystatin C as there is less difference between eGFRcys values for males and females and where there is now an option for computing eGFR without use of sex.

Together the set of statements allow for a consistent approach to the measurement and reporting of serum filtration markers and eGFR in clinical practice.

Jaffe methods	Enzymatic methods
acetaminophen[1] aspirin[1] ascorbic acid[77] bacterial contamination[78] bilirubin[79, 80] blood-substitute products[84] cephalosporins[85, 86] fluorescein[83] glucose[82] hemoglobin F[90] ketones/ketoacids[87] lipids[88] metamizole[1] protein[89, 90] pyruvate, including that arising from delayed sample processing[77] streptomycin[96]	bilirubin[146] lidocaine metabolites[51] metamizole[1] N-acetylcysteine[49] proline stabilizers, present in intravenous immunoglobulin preparations[50] phenindione[147]

Table 13. Reported examples of substances that may cause analytical interferences in creatinine assays. The nature of interference (magnitude and direction of bias) from the listed compounds is dependent on the precise reaction conditions in use, in relation to timing of spectrophotometric readings and chemical composition of the reagent: different versions of the Jaffe and enzymatic methods used by

different manufacturers will respond in variable ways to interferences. (Further information may be found in Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5-18.[144])

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 over the age of 2 years.

In the *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*,[1] a cut off of 60 ml/min per 1.73 m^2 was chosen to define "low" GFR for children. In this update, we advise increasing the cutoff to 90 ml/min per 1.73 m^2. In children, a compromised GFR is likely to deteriorate further, especially during periods of rapid growth in adolescence and warrants closer monitoring and early intervention. Even small decreases in eGFR (i.e., CKD G2) are associated with poor kidney outcomes. In a US study of over 7 million children captured by electronic health record data, 8600 had CKD G2. At 10 years from cohort entry, the rate of reaching kidney failure or a 50% decline in eGFR ranged from around 10% (non-glomerular CKD) to around 40% (glomerular CKD).[148] Furthermore, eGFR between 60 and 90 ml/min per 1.73 m^2 is sometimes associated with impaired linear growth and with hyperparathyroidism in children and adolescents.[149, 150]

A higher cut-off defining low GFR also reflects their long life expectancy. Early intervention may have profound protection of GFR. CKD G2 has long been considered to reflect decreased GFR in children, reflected by the inclusion of children with CKD G2 in pediatric CKD trials and cohort studies, including Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE),[151] Hypertension Optimal Treatment in Children with Chronic Kidney Disease (HOT-KIDS; United Kingdom [UK]),[152] CKiD (North America),[153] KoreaN cohort study for outcomes in patients with pediatric CKD (KNOW-PedCKD; South Korea),[154] and the Kids with CKD (KCAD; Australia and New Zealand). The definition of CKD remains unchanged, the flagging of GFR <90 ml/min per 1.73 m^2 as low for children and adolescents reflects the need for closer assessment and monitoring.

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). Within such regions, equations may differ for adults and children.

The recommendation places a high value on use of an estimating equation for GFR that has been validated in the population of interest and which has been shown to be most accurate in comparison to mGFR and a low value on the comparison of performance characteristics across different equations. The key points are to use an equation validated in and most suited to the population of interest.

Key information

Balance of benefits and harms

This recommendation recognizes that there are now a number of validated GFR estimating equations available. They have differing performance characteristics which may differ depending on the population of interest. The intention of suggesting the use of the same equation within a region is to reduce clinical confusion if people with CKD go to different laboratories within a region and to enable appropriate population comparisons. Use of different equations (and thus different eGFR values for the same person) may lead to confusion for both the individual person and their healthcare providers.

The Work Group judged that there is potential for harm if people get different eGFR values when receiving care in different settings. As described in Section 1.2.2, there are several sources of variability in eGFR. Differences between valid equations are often substantially less than these sources of variability, but that might not be understood by most healthcare providers or people, leading to excessive anxiety and repeated testing for small changes in GFR as related to use of a different GFR estimating equation. Using the same equation within the same geographical region, can eliminate the source of variation that is related to the specific parameters of the GFR estimating equation.

There is benefit to clinical care, research, and public health with the use of validated equations such that decisions, research findings, and public policy are informed by accurate estimates of CKD.

Certainty of evidence

This recommendation is based on Work Group consensus regarding good clinical practice to use a GFR estimating equation validated in the population of interest. Table 14 lists criteria for validated equations.

Criteria	Consideration
Developed using rigorous measured GFR (mGFR) methods; ideally using comparable measurements for all individuals in the development populations	Development methods
Developed using assays for filtration markers traceable to reference materials with acceptable accuracy and imprecision	Development methods
Developed with sufficient sample size for the population	Development population
Study populations with a wide range of clinical characteristics and GFR, where possible representative of the clinical populations in which equations are to be applied, including representative samples of general population and people with kidney disease	Development population
Performance vs. mGFR evaluated in separate populations from that in which it was developed (i.e., external validation, not random split of development data)	Accuracy
Performance shows certain thresholds for performance compared to other equations (see Table 13)	Accuracy
Can be reported by laboratories (i.e., no other variables required for computation that are not readily available)	Implementation by clinical laboratories

Table 14. Criteria for a validated glomerular filtration rate (GFR) estimating equation.

The criteria were developed by accumulated evidence from assessment of the performance of eGFR versus mGFR across equations and populations. For example, use of equations developed using assays that are not traceable to reference materials cannot be applied to settings with differences in assays,[155] or use of equations developed in one population may not perform well in other populations with very different characteristics.[90, 156, 157]

Values and preferences

There are now several valid equations that can be reasonably used in local settings. The Work Group recognizes that different values and preferences may lead to different decisions in selection among validated GFR estimating equations. Thus, instead of being prescriptive, we list a set of criteria that defines a valid equation, a set of equations considered valid at this time, and a list of metrics to define better versus worse performance as evaluated in the local area. It is a value that GFR thresholds for definition and staging be standardized using valid equations optimized for a specific region helps to ensure this occurs. Where possible, inclusion of representation from key constituents in the population in the development of the equation and ensuring that it remains valid in those populations is of value.

Using validated eGFR equations improves the accuracy of assessment of true GFR but remains imperfect and no single equation performs consistently across all populations. The Work Group judged that people with CKD and their healthcare providers would want GFR estimated using the equation providing the greatest accuracy in the population of their geographical region. The Work Group recognize that across the world there is significant variation in the sociodemographic and ethnic makeup of populations and that even well validated equations developed in different populations may not perform as well as others developed and validated in the population of interest.

Resource use and costs

There are minimal costs associated with implementation of a new equation. However, there are a number of initial costs including human resource costs associated with taking the time to decide on which equation, then time and technical information resources to be considered to change the computation and the laboratory and nephrology teams to test the new equation and inform the clinical partners on the change. In addition, education for primary care providers, people with CKD, and other healthcare providers is also required, which incurs both direct and indirect costs. There will be costs, both human resource and meetings costs, associated with decision-making around which equation to use. Additional costs will be accrued if validation and impact studies are required.

Considerations for implementation

Each region should have a mechanism for review and selection of equations for implementation by laboratories. For most countries, this might be through the national kidney society working in collaboration with laboratory physician organizations, or regional laboratory groups as has occurred in US and Europe, respectively.[158, 159] Decisions at this level by continental or national organizations are likely to minimize the likelihood that decisions for equation use will be made within small geographical areas or governed by local decisions, leading to greater variation in eGFR and uncertainty by people with CKD and healthcare providers. Considerations in decisions about implementation will reflect the balance of the criteria listed in Table 14.

There are likely to be tradeoffs between optimal accuracy in local regions versus uniformity. Equations optimized for a specific region can help to ensure that the GFR thresholds for disease definition, classification, and risk estimation have the same implications across regions. However, it would lead to barriers to implementation, as it will not be possible for all regions to conduct a sufficiently large and representative study to evaluate these equations and develop modifications. If not possible, or in the interim, we advise using equations that were developed in populations most similar to the available populations. For example, in Central or South America, it would be reasonable to use CKD-EPI given the inclusion of Black and Hispanic participants in the development of equation. It would be reasonable for other African

countries to use the Q-values (i.e., the minimum false discovery rate at which an observed score is deemed significant) developed in 2 African countries (thus to use EKFC) until ongoing efforts to develop African based equations are available.[156] We also note that if cystatin C is available, then using eGFRcr-cys would simplify the selection of the equation as the performance of eGFRcr-cys computed from the different equations is more similar than that of eGFRcr.

Frequent changes in the recommended GFR estimating equation may lead to inconsistency and variability between laboratories and may be predicated on responsiveness of the laboratory to adapt changes. Thus, carefully consider the frequency and need for changes in estimating equation, and embark on full educational programs to inform patients, healthcare providers, and laboratories as to the rationale and implications of those changes.

Rationale

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease recommended "to report eGFRcr in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation." We are updating this recommendation to accommodate the availability of alternative equations that also have high levels of accuracy. Since publication of the *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*[1] for GFR estimation in adults, there are 3 main sources of validated equations: those developed by the CKD-EPI, those developed by EKFC, and modifications of each for use in specific regions (Table 15). Table 16 lists thresholds for key performance metrics that can be used to guide comparison between equations.

The CKD-EPI Research Group developed equations for estimating GFR from creatinine and cystatin C, and the combination of creatinine and cystatin C, with and without inclusion of a coefficient for Black race. The concerns about the continued use of race in GFR that led to the removal of the race coefficient is described in the rationale that follows Practice Point 1.2.4.2. The 2009 CKD-EPI creatinine equation includes creatinine, age, race and sex.[81] The 2021 CKD-EPI creatinine equation was refitted without race and includes creatinine, age, and sex.[80] As a consequence of not including the Black race coefficient, the 2021 CKD-EPI creatinine equation leads to a small overestimate of GFR in non-Black individuals and a small underestimate in Black individuals. The 2009 CKD-EPI creatinine equation is more accurate than the 2021 CKD-EPI creatinine equation in the non-Black race group, as indicated by the percentage of eGFRs within 30% of mGFR (P_{30}), although the change in the level of accuracy is small compared to the known variability in mGFR and eGFR and P_{30} remains at the level consistent with recommended targets as indicated in listed in prior CKD guideline (Table 15, Section 1.2.2, Figure 9).[1, 80] The 2021 CKD-EPI eGFR creatinine-cystatin C equation that includes both filtration markers but

does not include a term for Black race leads to improved accuracy in both race groups, with less difference between race groups in all metrics.

The EKFC developed equations for estimating GFR from creatinine and cystatin C.[84, 160] Prior to implementation in other regions, the authors recommended that local regions specify population specific Q-values for the creatinine-based EKFC equation, which is the normal level of creatinine in that region. To make the SCr-based EKFC equation applicable for children, age adjusted Q-values were defined. The original EKFC creatinine equation had a Q-value developed from Belgium and Sweden but was validated in 7 European studies and is recommended for use in White Europeans.[160] They have recently published Q-values for Black Europeans developed from a cohort of 90 kidney donors in Paris and for Black Africans developed from 2 cohorts in République Démocratique de Congo Cote D'Ivoire. The EKFC cystatin C equation includes only age and cystatin C, that is, it does not include sex or race. The Q-value for cystatin C was developed in a White cohort in Uppsala, Sweden. The cystatin C-based EKFC equation has been validated in White Europeans, Black Europeans, White Americans, and Black Africans. To increase accuracy and precision, EKFC recommends averaging creatinine and cystatin C to obtain an estimate of GFR that includes both filtration markers. eGFRcr-cys (the average of the EKFC creatinine and EKFC cystatin C) also provides the most accurate estimates, consistent with the findings of CKD-EPI eGFRcr-cys.

In both the CKD-EPI and EKFC external validation datasets, there are consistent findings that the eGFRcr-cys provides improved performance in estimating mGFR compared to the respective creatinine or cystatin only equations. This reinforces the recommendation in Section 1.2.1 emphasizing greater use of eGFRcr-cys for decisions that require GFR.

There have been several modifications to the CKD-EPI equations for use in individual countries, including China, Japan, Pakistan.[89, 90, 157] We expect country-specific modifications of both CKD-EPI and EKFC to continue to be developed. One recent study in China reported no clinically meaningful difference in the performance of the Asian-modified CKD-EPI and EKFC equations compared with mGFR.[161]

Studies vary in their consistency and precision. Direct comparison of available estimating equations in populations with worldwide applicability are lacking and so too are validation studies comparing equations against mGFR in all populations of interest. The overall certainty of the evidence is therefore low but where the performance characteristics of GFR estimating equations in the population of interest are known there are data to support use of a one equation over another for improved accuracy of GFR reporting.

Marker	Equation name and year	Age	Variables	Development populations
Creatinine	CKD-EPI 2009[97, 98]	≥18; Modification CKD-EPI 40 for pediatric available	Developed using ASR but reported not using Black race coefficient, ASR (NB)	8254 Black and non-Black individuals from 10 studies in US and Europe*
	CKiD U25 2021	1–25	AS, height	928 children with CKD in US
	CKD-EPI 2021[98]	≥18	AS	8254 Black and non-Black individuals from 10 studies in US and Europe*
	EKFC 2021[162]	2–100	AS, European Black and non-Black specific Q-value; Separate Q-values for Africa vs. Europe	mGFR vs. SCr, (11,251 participants in 7 studies in Europe and 1 study from the US Normal GFR from 5482 participants in 12 studies of kidney donor candidates 100% Caucasian) European Non Black Q from 83,157 laboratory samples (age 2-40 years) in 3 European hospital clinical laboratories; European Black Q-value (N=90 living kidney donors from Paris); African Black Q-value (N=470 healthy individuals from République Démocratique de Congo); All Q-values developed in cohorts independent for EKFC development and validation
	Lund Malmo Revised[99]		AS	3495 GFR examinations from 2847 adults from Sweden referred for measurement of GFR
	CKD-EPI 2009 Modified for China 2014†	≥18	AS	589 people with diabetes from X Third Affiliated Hospital of Sun Yat-sen
	CKD-EPI 2009 Modified for Japan 2016†	≥18	AS	413 hospitalized Japanese people in 80 medical centers.
	CKD-EPI 2009 Modified for Pakistan 2013†[163]	≥18	AS	542 randomly selected low to middle income communities in Karachi and 39 people from the kidney clinic
Cystatin C	CKD-EPI 2012[164]	≥18	AS	5352 Black and non-Black individuals from 13 studies in US and Europe

	EKFC 2023[101]	18–100	A	mGFR vs. SCys (assumed to be the same as mGFR vs. SCr) Normal GFR (same as for SCr equation) Q from laboratory samples from 227,643 (42% Female) laboratory samples from Uppsala University Hospital, Sweden
	CAPA[102]		AS	4690 individuals within large subpopulations of children and Asian and Caucasian adults
Creatinine-cystatin C	CKD-EPI 2012[164]	≥18	Developed using ASR but reported not using Black race coefficient, ASR (NB)	5352 Black and non-Black individuals from 13 studies in US and Europe
	CKD-EPI 2021[98]	≥18	AS	5352 Black and non-Black individuals from 13 studies in US and Europe
	Average of EKFCcr and cys[101]	≥2	AS, European race specific Q-value; Separate Q-values for Africa vs. Europe	See above for EKFC creatinine and cystatin C

Table 15. Validated GFR estimating equations. *Also included 100 Asians and 353 Hispanic or Native Americans. †Modified from CKD-EPI or MDRD; Modifications may reflect systematic differences in measurement of creatinine and mGFR as well as population differences in nonGFR determinants of creatinine. A, age; CAPA, Caucasian and Asian pediatric and adult subjects; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; CKiD, Chronic Kidney Disease in Children; cr, creatinine; cys, cystatin C; EKFC, European Kidney Function Consortium; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate; NB, non-Black; R, race; S, sex; SCr, serum creatinine; SCys, serum cystatin C; US, United States

Criteria	Consideration
Systematic error (bias): Absolute magnitude of the absolute value of the median difference =|median (eGFR –mGFR)|	Small <5 Moderate 5–10 Large >10
Precision: IQR of the difference between eGFR and mGFR	Small <10 Moderate 10–20 Large >20
Accuracy: P_{30} (percentage of estimates within 30% of mGFR)	Optimal ≥90 Acceptable 80–90 Poor <80

Table 16. Criteria for equation comparison for comparison of candidate equations to another (i.e., how to determine validity). eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate. Units for systematic error (bias) and interquartile range (IQR) are ml/min per 1.73 m^2 and for units for P_{30} are percentages. Equations that have large error (bias) or IQR, or low P_{30} have poor performance.

Practice Point 1.2.4.2: Use of race as a distinct variable in the computation of eGFR should be avoided.

Estimating equations for GFR have historically incorporated demographic variables of age, sex, and race to explain variation in serum concentrations of endogenous filtration markers that are unrelated to GFR, thereby minimizing systematic errors in subgroups defined by these variables and systematic differences between groups.[165]

Age, sex, and race variables were included in the 2009 CKD-EPI equation as previous studies indicated higher average SCr for the same mGFR level in people who are older versus younger, males versus females, and people who are Black versus non-Black. Incorporation of these variables minimized systematic errors in groups and systematic differences between groups.[75, 165-167] Similarly, subsequent to the initial publication, EKFC developed additional Q-values for Black Europeans from Paris and Africans from Cote D'Ivoire and Democratic Republic of the Congo.

Race differs from age and sex, as race (and ethnicity) are dynamic, shaped by geographic, cultural, and sociopolitical forces, and thus the definition can change across geography and over time.[168, 169] Consistent with this, in the past several years inclusion of race in GFR estimating equations, along with other algorithms in medicine, faced increasing scrutiny, particularly in the US but also elsewhere in the world.[170-176] Concerns included, first, race is a social and not a biological construct, and thus the definition of a race group is subject to change over time. Second, using a binary variable to assign race groups ignores social and biological diversity within and among racial groups. For example, even if 2 people have the same genetic ancestry, living in different countries may indicate different nonGFR

determinants (i.e., observed variation between race groups may be specific to geographic region). Third, in countries with a high proportion of people who are Black, there are increasing number of people from mixed ancestry, thus leading to uncertainty was to how to apply the term and blanket use can lead to error.

Thus, even though the inclusion of race leads to improved accuracy compared to mGFR in some studies, these and other considerations led to the 2021 recommendation for it not to be used in the computation of eGFR in the US. Other countries have also recognized that race should not be included in computation and elected to use the CKD-EPI 2009 age, sex, race-non-Black (ASR-NB) as the population of people who are Black was sufficiently small to not warrant error for other groups. We recognize that specific countries or regions (e.g., Japan, Thailand) have developed "region specific" equations, which do not overtly use "race" as a variable but do advocate for modifying equations based on the population being tested.

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.

Examples of validated equations include the CKiD U25 2021 eGFRcr equation, the EKFC, and the CKD-EPI40. The Work Group judged that many healthcare providers would choose the CKiD U25 2021 eGFRcr equation given it was derived in a multiracial cohort of children with CKD and has been externally validated in cohorts with reduced and normal GFR. The performance of the CKiD U25 2021 eGFRcr equation is uncertain in the very young, those with very low GFR, or in populations outside of Europe and North America.[177] An alternative height/sex/age/creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates in the population of interest (Table 15). In children with neurological disorders, muscle-wasting, or who have metabolic disorders and are on a very low-protein diet, a cystatin-C-based equation is more appropriate.

1.3. Evaluation of albuminuria

Albuminuria refers to abnormal loss of albumin in the urine (urine ACR >30 mg/g or ≥3 mg/mmol). Albumin is one type of plasma protein found in the urine in normal subjects and in larger quantity in people with kidney disease. In the *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*,[1] clinical terminology was changed to focus on albuminuria rather than proteinuria as albumin is the principal component of urinary protein in most kidney diseases.[1] Epidemiologic data demonstrate a strong relationship between the quantity of urine albumin with both kidney and CVD risk and observed CVD even at very low levels; and assays to measure albumin are

more precise and sensitive than assays to measure urine protein. We refer to albuminuria or urine albumin when discussing general concepts and will refer either to total protein, albumin, or other specific proteins when discussing that parameter specifically.

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 mid-stream sample is preferred in adults and children.

6. **urine ACR**
7. **urine protein-to-creatinine ratio (PCR)**
8. **reagent strip urinalysis for albumin and ACR with automated reading**
9. **reagent strip urinalysis for total protein with automated reading**
10. **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 mid-stream 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 (Table 17).

	Factor	False positive	False negative
Variability in urine albumin or protein	Hematuria	Increases albumin and protein in the urine	
	Menstruation	Increases albumin and protein in the urine	
	Exercise[54]	Increases albumin more than other proteins in the urine	
	Infection[55, 56]	Symptomatic urinary infection can cause production of protein from the organism.	
	Non-albumin proteins		Other proteins may be missed by albumin reagent strips
Variability in urinary creatinine concentration	Biological sex	Females have lower creatinine excretion, therefore higher ACR.	Males have higher creatinine excretion, therefore lower ACR.
	Weight[57, 58]	High creatinine excretion consistent with high weight can cause low ACR or PCR relative to timed excretion	Low creatinine excretion consistent with low weight can cause high ACR or PCR relative to timed excretion
	Changes in creatinine excretion	Lower urinary creatinine concentration with AKI	Increased urinary creatinine concentration with meat intake or exercise

Table 17. Factors causing biological variation in urine albumin or urine protein. ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; PCR, protein-to-creatinine ratio

The practice point advocating for the use of spot samples measuring albumin or protein greatly facilitates its incorporation into clinical practice by avoiding the need for timed urine collections. Such spot samples can over- or underestimate urine albumin due to variation in dilution. Use of ACR or PCR in spot urine samples can decrease this error. ACR is an estimate of total urine albumin loss. Creatinine excretion rate varies substantially between people. ACR or PCR will overestimate urine albumin loss in people with low creatinine excretion and will underestimate urine albumin or protein loss in people with very high creatinine excretion.

The decision by prior guideline Work Groups not to have a sex-specific threshold and to use easy-to-remember values regardless of units also may lead to some misclassification. On balance, the current Work Group agrees with this approach given the continued underutilization of urine albumin in assessment of CKD.

It is possible that replacing urinary total protein measurement with albumin measurement may cause non-albuminuric (effectively tubular and overproduction) proteinuria to be missed. The significance of this issue is thought to be low in adults.[54-56, 178]

In health, relatively small amounts of albumin (<30 mg/24 hours) are lost in the urine. Urine albumin measurement provides a more specific and sensitive measure of changes in glomerular permeability than urinary total protein.[179-181] There is evidence that urinary albumin is a more sensitive test to enable detection of glomerular pathology associated with some other systemic diseases including diabetes, hypertension and systemic sclerosis.[182-185]

Total protein measurement is problematic in urine due to imprecision and insensitivity at low concentrations - relatively large increases in urine albumin loss can occur without causing a significant measurable increase in urinary total protein;[181] large sample-to-sample variation in the amount and composition of proteins; high and variable concentrations of non-protein interfering substances relative to the protein concentration; and high inorganic ion content. Most laboratories currently use either turbidimetry or colorimetry[186] to measure total protein. These methods do not give equal analytical specificity and sensitivity for all proteins, with a tendency[186-188] to react more strongly with albumin than with globulin and other non-albumin proteins,[189-192] and many have significant interferences causing falsely high results.[192-194] There is no reference measurement procedure and no standardized reference material for urinary total protein measurement (https://jctlm.org/). The variety of methods and calibrants in use means that there is inevitably significant between-laboratory variation.[195-197]

Studies examining the diagnostic accuracy of tests to quantify urine albumin and other proteins usually compare tests to laboratory quantification from 24-hour urine collections. It is generally recognized that a 24-hour sample is the definitive means of demonstrating the presence of albuminuria. However, timed samples are often collected with error. Overnight, first void in the morning, second void in the morning, or random sample collections are therefore recommended as first line tests.[198, 199] Since creatinine excretion in the urine is fairly constant throughout the 24-hour period, measurement of ACR (or PCR) allows correction for variations in urinary concentration.[200, 201] ACR is a suitable alternative to timed measurement of urine albumin loss.[202-207] PCR on random or early morning untimed samples shows good diagnostic performance and correlation with 24-hour collection.[198, 208-215]

We acknowledge that reagent strip devices can have a role in settings where access to laboratory services may be limited (see Section 1.4).

Implementation of first morning voids will be difficult to obtain in most healthcare settings. Nephrology offices could develop protocols to send people with CKD home with a urine collection container and instruction on how to obtain a clean catch, which the person brings back before their next visit. Alternatively obtaining blood and urine tests prior to the next visit can facilitate first morning voids. However, in the absence of a first morning voids, a random sample may still be used. Negative findings in people at high risk for CKD, for example where the urine sample is diluted, can be confirmed with a subsequent first morning void. Positive findings in people at low risk for CKD, where the ACR level is just above the threshold where the urine samples is concentrated, can also be confirmed with a first morning void.

The numeric equivalence of ACR in mg/g (mg/mmol) to ~g/day is based on the simple assumption that creatinine excretion rate (CER) approximates 1 gram/day (10 mmol/day). To better estimate urine albumin in individuals with creatinine generation that is very different from the average, one might consider measuring a timed urine collection if the value would affect clinical decisions. As with assessment of GFR using measured CrCl, use supervised urine collections. Alternatively, equations are available which estimate creatinine generation from prediction equations and then multiply that value by the ACR to compute an estimated albumin excretion rate (AER) that accommodates the lower or higher level of CER.[216, 217]

Measurement of urinary albumin is recommended because it is relatively standardized and because it is the single most important protein lost in the urine in most chronic kidney diseases. Use of urinary albumin measurement as the preferred test for proteinuria detection will improve the sensitivity, quality, and consistency of approach to the early detection and management of kidney disease.

Commonly used reagent strip devices measuring total protein are insufficiently sensitive for the reliable detection of proteinuria, do not adjust for urinary concentration, and are only semi-quantitative. Furthermore, there is no standardization between manufacturers. The use of such strips should be discouraged in favor of quantitative laboratory measurements of albuminuria or proteinuria, or validated point-of-care devices for urine albumin/ACR (Section 1.4). When used, reagent strip results should be confirmed by laboratory testing.

Although the reference point remains the accurately timed 24-hour specimen, it is widely accepted that this is a difficult procedure to control effectively and that inaccuracies

in urinary collection may contribute to errors in estimation of albumin and/or protein losses. In practice, untimed urine samples are a reasonable first test for ascertainment of albuminuria. A first morning void sample is preferred since it correlates well with 24-hour albumin and/or protein excretion, has relatively low intra-individual variability, and is required to exclude the diagnosis of orthostatic (postural) proteinuria. A random urine sample is acceptable if no first morning void sample is available. The concentration of albumin or protein in a urine sample will be affected by hydration (i.e., how diluted or concentrated a urine sample is), and reporting the albumin or protein to the creatinine ratio will correct for urinary concentration and reduce intra-individual variability.[144, 178, 218, 219]

There is biological and analytical variability in urine albumin and urine protein loss. There are several biological factors which affect urine albumin or protein loss, separate from kidney disease (Table 16).[55] All of these can lead to false detection of CKD or its progression. Thus, positive tests should be confirmed, especially in people without risk factors for CKD. Large changes would be repeated to confirm increasing urine albumin and urine protein. Chapter 2 discusses the magnitude of change to be considered a real change given the known biological and analytical variability.

There is also biological variability in urine creatinine excretion. Change in creatinine concentration in the urine can also lead to observed changes in ACR or PCR, independently of changes in protein loss. In general, urine creatinine measurements are less susceptible to factors that interfere with SCr assays. If a more accurate quantification of albuminuria or total proteinuria is required, measure urine albumin or total protein in a timed collection under supervised conditions as recommended above.

Special considerations

Pediatric considerations

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

5. **urine PCR**
6. **urine ACR**
7. **reagent strip urinalysis for total protein with automated reading**
8. **reagent strip urinalysis for total protein with manual reading.**

Consistent with the *KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*,[1] PCR is advised and preferred as initial screening for children as the majority of children have underlying developmental abnormalities often referred to as CAKUT (congenital anomalies of the kidney and urinary tract) and a much higher proportion of children than adults have tubular pathology.[220] Testing for ACR may miss tubular proteinuria.

The same considerations of using first morning samples (because of orthostatic proteinuria) and considering transiently increased proteinuria during intercurrent illness or after exercise apply to children as well as adults. Orthostatic proteinuria is estimated to affect 2%–5% of adolescents.[221]

Age and body size are important for interpreting proteinuria. In term and preterm neonates, PCR is high (PCR 1000–3000 mg/g [100–300 mg/mmol]) in the first days and weeks of life and is related to glomerular and tubular losses of protein from immature nephrons, as well as very low creatinine from low muscle mass. Recent studies outline proteinuria ranges for neonates, including for preterm and low birth-weight neonates. As the tubules mature, proteinuria slowly declines. In general, a PCR of <500 mg/g (<50 mg/mmol) (or a 24-hour protein of <150 mg/m^2/day) is considered normal for infants 6 months to 2 years. For children over 2 years, a first morning urine PCR of <200 mg/g (<20 mg/mmol) protein, or <150 mg/m^2/day, or a first morning urine ACR <30 mg/g (<3 mg/mmol) is usually considered normal.[89, 222-225] More comprehensive values can be found in *Pediatric Nephrology*.[226]

1.3.2. Guidance to clinical laboratories

The following comments are focused on the laboratory assessment of albuminuria, rather than total proteinuria, given albumin measurement is the preferred approach to proteinuria evaluation (Section 1.3.1.) However, some of these practice points (sample type and storage, reporting as a PCR) would apply equally to total protein measurement practices.

Practice Point 1.3.2.1: Implement the laboratory reporting and handling standards outlined in Table 18 to ensure accuracy and reliability of the findings when assessing urine samples.

• Samples analyzed fresh or stored at 4ºC for up to 7 days.
• Samples should not be stored frozen at -20ºC.
• Report ACR in untimed urine samples in addition to urine albumin concentration rather than the concentrations alone.
• Reporting to one decimal place for ACR whether mg/mmol or mg/g
• Analytical CV of methods to measure urine albumin should be <15%.

Table 18. Implementation standards to ensure accuracy and reliability of urine samples. ACR, albumin-to-creatinine ratio; CV, coefficient of variation

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

Adoption of the reporting and handling standards for assessment of urine samples is of paramount importance to ensure that healthcare providers receive urine ACR reports in a consistent style and with assurance regarding the accuracy and reliability of the result.

Measurement of urine albumin for the detection of kidney disease as with any analyte should be with methodology traceable to international standards using a standard reference material. This is currently not the case and results may vary by greater than 40% between laboratories depending on the methodology used with attendant impact on the interpretation of reported results.

The type of urine collection and the analytical method influences result interpretation. 24-hour urine collections present problems in terms of completeness of collection, specimen storage and timing accuracy. Therefore, assessment of ACR from a single void is a common and convenient clinical practice. The ACR accounts for hydration and has similar diagnostic performance to 24-hour urine AER. The collection method should remain consistent, preferably using the first morning void specimen.

If specimens are being stored for future analysis careful attention must be paid to the storage conditions to avoid degradation of albumin leading to quantification error. The reported effects of frozen storage on urine albumin are somewhat inconsistent. Albumin is generally stable in urine stored at 2–8ºC for 7 days. However, losses of albumin have been reported when urine is stored frozen at temperatures higher than -80ºC. Precipitates often form when urine is stored refrigerated or frozen but can be redissolved on warming: samples should be warmed to room temperature and mixed before analysis.[207] Albumin losses may be affected by factors including period of storage, sample albumin concentration and individual variation.[227] It should be possible to provide refrigerated storage and process samples for albumin measurement in a laboratory within 7 days in most healthcare settings.

The internationally accepted laboratory quality standards are variably met worldwide and laboratories are at different levels with respect to quality. However, the Work Group placed a high value on the accuracy and reliability of quantification of albuminuria and judged that people with CKD, their healthcare providers, and policy makers would want laboratories to achieve these reporting and handling standards.

The direct costs of total protein measurement in urine are lower than those of urine albumin. However, total protein measurement lacks sensitivity for the detection of low but clinically significant levels of albuminuria. For this, and other reasons discussed in Section 1.3.1, the measurement of ACR is preferred to that of PCR.

Urine albumin should be measured using immunological assays capable of specifically and precisely quantifying albumin at low concentrations and of producing quantitative results over the clinically relevant range. The biological variation of urine albumin exceeds 60%. Target analytical variation (CV) should be based on an optimal level of <0.25 biological variation, approximately 15%. This is in keeping with good practice recommendations from the National Academy of Clinical Biochemistry.[228]

Significant progress has been made in developing a certified reference material for urine albumin and a reference measurement procedure.[229, 230] However, current commercially available assays for urine albumin are not standardized against this reference material. Laboratories should ensure that they are enrolled, and demonstrate satisfactory performance in, an external quality assessment scheme for urine albumin, creatinine and ACR.

Urine albumin (and protein) concentrations in urine should be reported as a ratio to creatinine – ACR (or PCR). Reporting as a ratio to creatinine corrects for variations in urinary flow rate and enables reporting on untimed, spot samples, obviating the need for timed, including 24-hour, collections, which are prone to collection error and tedious for people to undertake. Reporting albumin as a ratio to creatinine reduces the intraindividual variability in albuminuria compared to reporting as albumin concentration alone (mg/mmol or mg/g).[231]

To aid clarity in reporting across and within healthcare systems, and to provide guidance regarding the number of meaningful digits in a result, a standardized approach should be used in relation to reporting units of ACR and PCR. ACR results should be expressed to one decimal place (mg/mmol) or whole numbers (mg/g). Both enzymatic and Jaffe assays are generally suitable for the measurement of creatinine in urine, although high concentrations of glucose can interfere in Jaffe urine creatinine measurement and produce clinically meaningful errors in ACR.

1.4. 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 that is 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 95% of people with significant albuminuria (ACR ≥30 mg/g or ≥3 mg/mmol), as part of the evaluation and consideration of using the device.

This recommendation places a high value on the advantages of point-of-care tests including convenience, elimination of sample transportation to the central laboratory, minimal sample processing, simple analytic process, minimal sample requirement, and immediate availability of results. It places a lower value on the limited and heterogeneous data related to their diagnostic accuracy.

Key information

Balance of benefits and harms

POCT for both creatinine and urine albumin have several potential benefits. POCT testing may lead to earlier diagnosis, and as a result, earlier treatment of CKD. They may also be used to monitor CKD progression which enables more timely treatment decisions. The rapid reporting, low cost, and convenience to people with CKD compared with central laboratory testing are also important benefits of POCTs. However, its provision can raise challenges in relation to maintenance of analytical and diagnostic performance, and governance arrangements. Additionally, these tests may be less accurate than laboratory testing which may lead to misdiagnosis, misclassification, overtreatment, or undertreatment. The balance of benefits and harms needs rigorous evaluation specific to each clinical situation.

For creatinine, the ERT identified a systematic review from the National Institute for Health and Care Excellent (NICE)/National Institute for Health Research (NIHR) diagnostic guideline that evaluated point-of-care creatinine tests to assess GFR prior to computed tomography (CT) scanning with contrast media.[232] The ERT also updated the findings of this systematic review. The review from NICE/NIHR identified and qualitatively synthesized data from 54 studies on diagnostic accuracy: eGFR diagnostic accuracy (n=12); SCr diagnostic accuracy (n=7); and correlation and bias of POC creatinine tests compared to laboratory-based tests (n=50). One study[233] was identified in the update of the NICE/NIHR review assessing POC creatinine test compared to laboratory standards in a pediatric population with malaria in Uganda.

These studies covered 3 types of device: StatSensor, i-STAT and ABL devices. In general, all 3 devices demonstrated acceptable accuracy at lower levels of eGFR (<30 ml/min per 1.73 m^2).[232] Results showed that i-STAT and ABL devices may have higher probabilities of correctly classifying people in the same eGFR categories as the laboratory reference than StatSensor devices.

For albumin, the ERT identified a systematic review published in 2012, by McTaggart *et al*., that evaluated the diagnostic accuracy of quantitative and semi-quantitative protein or albumin urine dip stick tests compared to laboratory-based tests among people with suspected or diagnosed CKD.[234] They included relevant studies from this review and conducted an update.

Sixty-five studies (in 66 articles)[235-253, 254#, 255-278, 279#, 280-300] evaluated the accuracy of quantitative and semi-quantitative protein or albumin dip stick tests in a general population not on KRT or receiving end-of-life care. Studies addressed the following critical outcomes: measurement bias (n=1); analytical variability (n=5);.analytical sensitivity (n=2); and analytic specificity (n=63) (Supplementary Table S5). Specificity ranged from 17.5–99.5 when evaluative ACR ≥30 mg/g, 30.0–98.7 when evaluative ACR ≥300 mg/g. For PCR, specificity ranged from 80.8–96.9 when evaluative PCR >200 mg/g and 75.6–95.2 when evaluative PCR >500 mg/g.

The evidence regarding performance of POCT testing for creatinine and urine albumin is heterogenous limiting the determination of overall findings across these critical outcomes. However, given the cost-effectiveness benefits, availability of the test in the absence of laboratory studies, and the acceptable test performance, the Work Group judged that in specific clinical scenarios, POCT testing should be used.

Certainty of evidence

The certainty of evidence for POCT for creatinine testing was rated as low due to consistent reporting of reference standards across all outcomes, with some concerns regarding patient selection and flow and timing and directness of the evidence. The certainty of evidence regarding performance of all POCT for urine albumin was very low based on the QUADAS-2 assessment of individual studies due to sparse data, heterogenous findings, and concerns about patient selection, index tests and unclear reporting of the reference standards.

Values and preferences

The recommendation suggested that the majority of people with CKD who have limited access to laboratories would choose to use POCT. These tests may facilitate people with CKD being seen at home or in remote settings. Many people with CKD will value the immediate results available with POCT versus waiting for the tests by a lab. Additionally,

some people with CKD will place a higher value on avoiding expensive lab tests that may not be covered by their insurance, difficult travel to central healthcare facilities, and exposure to infection risk in hospital. These people with CKD may also place a lower value on the potential inaccuracies associated with POCTs compared to in-center laboratory testing.

Resource use and costs

For people with CKD, the use of POCTs may be less expensive than tests conducted in a clinical laboratory. In areas with limited access to healthcare and insurance, these tests may be cost saving. For the healthcare system, some direct reagent and staff costs of POCT tend to be higher on a per test basis than those of centralized laboratory testing, but these costs may be offset by other savings in the clinical pathway, for example through more rapid disease detection or avoidance of hospital referral.

Considerations for implementation

Support from the local laboratory service should be sought to guide the purchase, evaluation, implementation, governance, and ongoing quality assurance of POCT. The ability to test creatinine in a person's home may have applicability to "virtual ward" settings (hospital at home).

It is worth noting that for albuminuria testing, the National Academy of Clinical Biochemistry has proposed that devices should have 95% sensitivity for the detection of albuminuria.[228] This is not always achieved by POCT devices, especially those which produce semiquantitative results.[234]

Rationale

POCT can be carried out in a wide range of settings including primary care, community clinics, rural communities, and secondary care supporting timely diagnosis, monitoring, and treatment. Importantly, in locations where laboratory services may be limited or non-existent (e.g., rural and remote communities), the ability to test at all versus not testing blood and urine was important. Advantages of POCT testing include convenience, elimination of sample transportation to the central laboratory, minimal sample processing because the analysis is of whole blood/urine, simple analytic process, and minimal sample requirement and immediate availability of results. However, these tests may be prone to errors and inaccuracies. For these reasons, the recommendation suggests the use of these test based on the specific clinical need or geographical/social circumstances.

Special considerations

Pediatric considerations

The ability to use a small sample volume, fingerprick sample as opposed to venepuncture may have applicability to testing in children.

CHAPTER 2. RISK ASSESSMENT IN PEOPLE WITH CKD

2.1. Overview on monitoring for progression of CKD based upon GFR and ACR categories

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

Monitoring CKD through surveillance of albuminuria and GFR serves to update staging for prognosis, identify timing of intervention strategies and assess the effectiveness of specific treatments. No clear threshold defines a clinically relevant change in GFR or albuminuria, as any worsening could reflect deterioration in kidney health. However, overinterpretation of small changes in these measures may lead to unnecessary changes in clinical management that could be unhelpful or even deleterious. Education for healthcare providers and people with CKD about the variability of specific laboratory measurements in kidney disease is important to facilitate understanding and to mitigate inappropriate changes in treatment strategies due to non-clinically significant fluctuations in either positive or negative directions.

There is an expected variability in GFR caused by both biological and analytical factors of the biomarkers used (Figure 8). We have chosen to consider the 95% confidence interval of test reproducibility for both eGFR and ACR as an important factor for determining thresholds for clinical evaluation. Initial evaluation of an observed changes in either eGFR or ACR should be to repeat the test(s) so as to determine if the observed change is clinically significant progression of CKD or is within biological and analytical variability of the test.

Special considerations

Pediatric considerations

Monitoring of children in the peripubescent phase should be undertaken more frequently than the CKD stage-based recommended frequency of monitoring as puberty is a period of high risk of progression.[301] Reasons for this are incompletely understood, but potential mechanisms include inability of diseased kidneys to undergo the hypertrophy needed to accompany the rapid somatic growth that characterizes puberty and the negative effect of increased levels of sex steroids.[302] A study of over 900 children with CKD due to congenital anomalies of the kidneys and urinary tract showed a decline that was >10-times faster in creatinine-based eGFR after the period of peak growth than before that period.[302] The CKiD study (including children with CKD of any cause) showed more rapid declines in both eGFR (creatinine- and cystatin C-based) and mGFR after the period of peak growth velocity than before.[301] Frequency of monitoring should be individualized, and informed by the severity of CKD, stage of puberty, and observed recent rate of progression.

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.

Previous guidelines have suggested routine monitoring of albuminuria and GFR. Prior guidelines have suggested annual monitoring for those with CKD G1–G2, every 6 months for those with CKD G3, every 3 months for CKD G4, and every 6 weeks for CKD G5 disease. Given the greater risk of disease progression, those with higher risk of disease progression should undergo more frequent monitoring (Figure 10). More frequent monitoring may be indicated in people with changing clinical status, intercurrent events, and after therapeutic interventions to assess response and adherence and ensure safety.

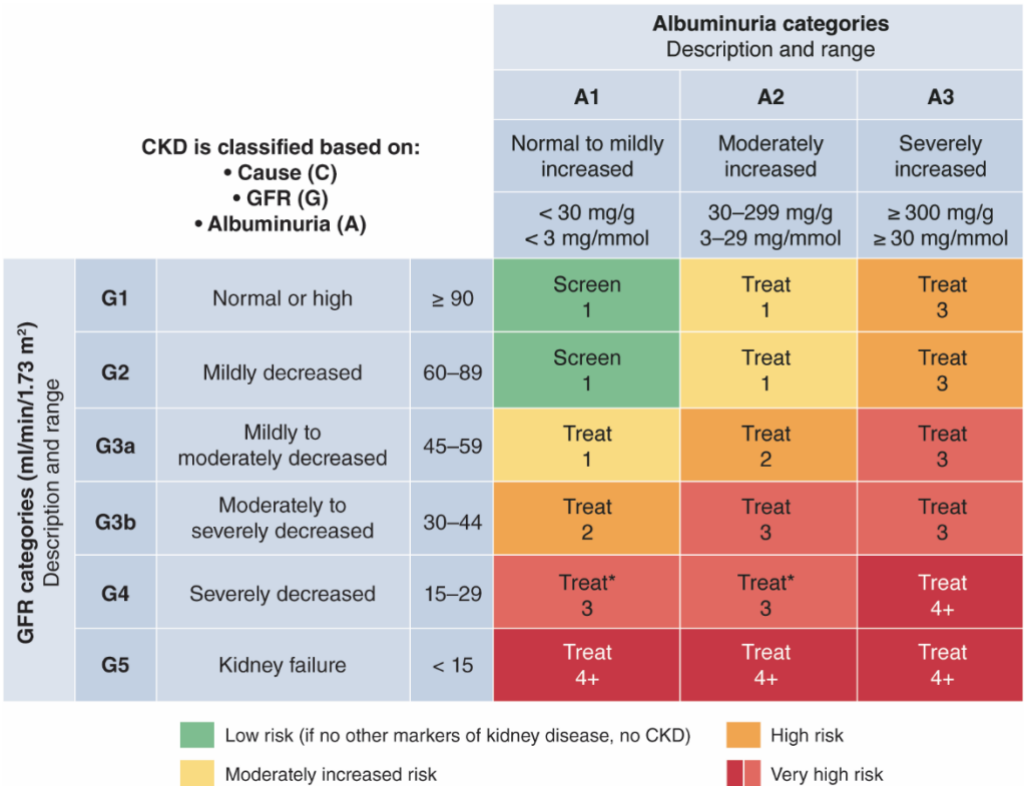


Figure 10. Frequency of glomerular filtration rate (GFR) and albuminuria in people with chronic kidney disease (CKD). Albuminuria and GFR grid reflects the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Reproduced from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2022; 102: 974-989.[303]

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.

Within subject variation in measured and eGFR is well described (Figure 8). Thus, the ability to distinguish between biological and analytical versus pathological variation in the

mGFR and eGFR is important for healthcare providers and people with CKD. Studies show that intraindividual biological variation in eGFR is similar across eGFR equations: CKD-EPI-creatinine (5.3% [4.5–6.4]), CKD-EPI-cystatin C (5.3% [4.5–6.5]), and CKD-EPI-creatinine-cystatin C (5.0% [4.3–6.2]). The reference change value (RCV) is defined as the threshold of change that differs from the individual's prior value with 95% confidence; in a cohort of people with CKD, eGFRcr and eGFRcys had RCVs ranging from 14%–20% in the positive and negative directions. Whilst attention to progressive loss of eGFR is important, smaller changes in GFR may not be related to true changes in kidney health, especially if transient and require cautious interpretation.

Thresholds for CKD progression used in clinical trials and epidemiological studies are different than those suggested for monitoring of people with CKD. In research studies, 30%–40% declines in GFR have been associated with increased risk for kidney failure, and treatment effects on these endpoints have been associated with changes in risk for kidney failure. Because these are evaluated at the group level, small errors in individual people with CKD are minimized.

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.

Acute eGFR decline following intensive BP control have been observed in people with CKD, with reductions of 10%–20% being typical within the first 3 months of treatment. These declines in eGFR are hemodynamically moderated, a response to BP falling below the lower threshold of a person's autoregulatory response. For many, this initial decline in eGFR is transient and will stabilize or resolve over time, as resetting of the autoregulatory function occurs. Thus, acute rises in SCr (or declines in eGFR) of <20%–30% are expected and do not warrant changes in therapeutic agents, which may be important for cardio- and kidney protective effects in the long term. This phenomenon is especially common when using ACEi/angiotensin II receptor blockers (ARBs), as they both lower BP and alter arteriolar flow through the glomeruli, and SGLT2i through similar hemodynamic mechanisms.

Post hoc analyses of trials of SGLT2i treatment in people with diabetes, heart failure, and CKD suggested that participants with >10% initial drop in eGFR have similar eGFR trajectories and kidney benefits from SGLT2i compared to the "non-dipper" who received SGLT2i, except in unusual cases when the acute "dip" in eGFR was >30% from baseline.[304, 305] These findings were consistent across all subgroups.

A significant drop in eGFR (>30%) while initiating antihypertensive agents, renin-angiotensin system inhibitors (RASi) or SGLT2i should prompt a review into other causes and warrants close monitoring. However, healthcare providers should avoid the urge to stop these

kidney-protective agents, particularly since these earlier “dips” are typically reversible and not an indication of drug toxicity.

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.

Small fluctuations in albuminuria levels may not indicate disease progression. Appreciation of factors that impact albuminuria and changes in the measure is important for healthcare providers. Routine surveillance using ACR or protein-to-creatinine ratio (PCR) is warranted in higher risk people with CKD, as changes in urine ACR are associated with kidney failure. Specifically, in large population studies, a doubling of the ACR within a 2-year duration is associated with an increase in the risk of progression to kidney failure by 50%–100%.[306, 307] However, changes in albuminuria within an individual have substantial variability, with large fluctuations expected given that the 95% confidence interval around repeat ACR testing is about 50%. For this reason, the Work Group has defined a doubling in albuminuria or more as exceeding the expected variability and warranting evaluation if replicated upon repeat testing. Conversely, reductions of the ACR by up to 50% are also consistent with random fluctuation.

Special considerations

Pediatric considerations

Increases in albuminuria and proteinuria are also associated with increased risk of disease progression in pediatric populations. A number of studies in pediatric subjects detailed in Table 19 highlight the value of measurement of albuminuria/proteinuria.

Study	Impact of albuminuria/proteinuria
ESCAPE[151]	50% reduction of proteinuria within the first 2 months of treatment initiation more than halved the risk of progression of kidney disease over 5 years.
Gluck et al.[148]	In a cohort of over 7 million children, 0.1% had CKD G2 or higher. The relative risk of CKD progression, defined as reaching CKD G5 or having a 50% decline in eGFR, was doubled for those who had ≥1+ proteinuria on dipstick without hypertension and was quadrupled for those with proteinuria and hypertension over a median follow up of 5 years.
CKiD[308]	ACR of >300 mg/g (>34 mg/mmol) was associated with an 84% higher risk of disease progression over a median follow up of 3 years compared to an ACR of 30 mg/g (3 mg/mmol). PCR of 630 mg/g (70 mg/mmol) was associated with an 87% higher risk of disease progression, compared to a PCR of 140 mg/g (15 mg/mmol).
4C study[309, 310]	Each log higher value of ACR was associated with a 50% higher risk of kidney failure or 50% decline in eGFR over a median follow up of 3 years. A 115% increase in albuminuria associated with faster disease progression after cessation of RASi in children with advanced CKD.
ItalKids[311]	Significantly slower decline in creatinine clearance in patients with baseline PCRs of <200 mg/g (<20 mg/mmol) and 200–900 mg/g (20–90 mg/mmol) when compared to those with a PCR of >900 mg/g (>90 mg/mmol). This translated to higher rates of kidney survival over 5 years in the lower proteinuria groups: 97% and 94% versus 45%.
Indian cohort[312]	CKD progression risk within 2 years was tripled for those with proteinuria >2000 mg/g (220 mg/mmol).
Japanese cohort[313]	Risk of CKD progression was 7 times as high for those with proteinuria >2000 mg/g (>220 mg/mmol) compared to those with lower proteinuria concentrations after adjustment for CKD stage, hypertension, sex, and age.

Table 19. Impact of albuminuria/proteinuria on chronic kidney disease (CKD) progression in pediatrics. ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio

Considerations in older adults

Urine ACR in older adult population may be elevated due to loss of muscle mass leading to lower SCr and lower urinary creatinine clearance (CrCl). In older adults or people with frailty, the interpretation of urine ACR should take into consideration age-related changes in muscle mass and/or sarcopenia.

2.2. Risk prediction in people with CKD

The CKD staging heatmaps reflect relative risks for each CKD category compared with persons who do not have CKD at a population level; however, a person's absolute risk for each outcome requires the use of risk prediction equations for the specific adverse event.

Individual level risk prediction can inform key clinical decisions, improve the patient-healthcare provider dialogue, and enable personalized care for persons with CKD.[314] The heatmap concept introduced in the KDIGO 2012 CKD guideline emphasizes the relative risk of adverse outcomes by levels of eGFR and albuminuria in populations, and encourages healthcare

providers to classify those people with CKD as high risk for kidney, cardiovascular, and other adverse events based on those 2 parameters.[315] The heatmaps also reinforce the importance to all of using both eGFR and ACR for assessing severity and prognosis of CKD and are color-coded to indicate those relative risks in populations but do not enable individual risk prediction.

However, the people within a specific "cell" on the grid or within an eGFR/ACR category have a wide range of absolute risks for each of the adverse outcomes of interest. An individual person's risk for each outcome is influenced by their underlying etiology of CKD, demographic characteristics, comorbid conditions, and other factors including lifestyle, socioeconomic status (SES), nutrition, and intercurrent events. Thus, the relative risks shown in the heatmap tables can be crudely interpreted as a multiplier superimposed upon the aforementioned other characteristics. There can be substantial variability and overlap, up to 8000% in the risk of CKD progression, or 4000% in the risk of kidney failure for 2 people in the same heatmap category or CKD stage (Figure 11);[316] therefore individual risk prediction using accurate and externally validated risk equations is important in the personalization of care and can be used to inform absolute risk for individual patients.

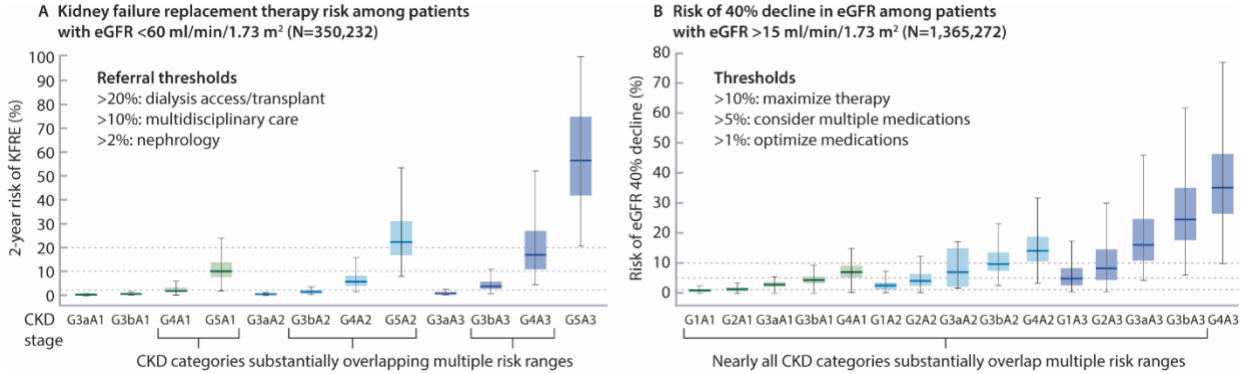


Figure 11. Predicted risk of kidney failure (panel A) and ≥40% decline in estimated glomerular filtration rate (eGFR) (panel B) by chronic kidney disease (CKD) eGFR (G1 to G5) and albumin-to-creatinine ratio(ACR) (A1 to A3) stage in Optum Labs Data Warehouse. Lines show potential thresholds for clinical decisions

The corollary to individualizing absolute risks vs relative risks, is appreciating absolute vs relative benefits of disease modifying therapies. While the relative benefits of medications such as SGLT2i may appear similar across subgroups, the actual benefit on specific outcomes is highest among people who have the higher absolute risks for that outcome.[317] Risk prediction equations can be used to better identify these people and perform better than healthcare provider subjective estimation of risk.[318] Several risk prediction tools have been developed specifically for people with CKD, and when implemented, allow healthcare providers to more precisely estimate risk for individual people for specific outcomes, which supports a deeper personalization of CKD management.[319, 320] Besides improving individual risk prediction, these tools may be used to more effectively use specialized and often scarce, nephrology resources, identify people for earlier use of disease-modifying therapy, or enable personalized discussions of overall goals of care. Importantly, some of the developed prediction models have been externally validated in

multiple populations, have high discrimination performance (C statistics >0.8 or higher), and are easily used via online calculators (Table 20).

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).

This recommendation places a high value on the need and potential benefits for individual risk prediction to deliver personalized care for people with CKD. The recommendation is worded to encourage healthcare providers, patients, researchers, and policy-makers to go beyond broad categories of relative risk for population, and to estimate the absolute risk of outcomes for each individual. The recommendation also places a high value on externally validated prediction equations that can be applied in diverse healthcare settings and the need for implementation science in laboratory information systems and electronic medical records to enable the delivery of risk-based care for people with CKD.

Key information

Balance of benefits and harms

There is a large body of evidence to support the use of the validated risk equations to estimate the absolute risk of kidney failure requiring dialysis or transplant in individuals with G3–G5. Risk equations using routinely collected data have been developed, externally validated, and implemented in labs, electronic medical records, and health systems.[321-323]

Multiple systematic reviews and quality assessments of risk prediction equations have been performed in the last 10 years, with the most recent review published in 2020.[319] This review included 35 development studies and 17 external validation studies, and described the variables included in the prediction models, and provided a decision aid for selecting the best model for the prediction horizon and the underlying etiology of kidney disease. More recently, an additional externally validated model using serum cystatin C has also been developed in Germany and externally validated in 3 European cohorts.[324] A summary of externally validated models for kidney failure is provided below and in Table 20.

Equation	Variables	Population	Outcome Time horizon	Discrimination and calibration	Usability
KFRE[9, 10, 323, 325] www.kidneyfailurerisk.com www.ckdpc.org/risk-models.html	Age, sex, eGFR, ACR (4 variable) + Calcium, Phosphate, Bicarbonate and Albumin (8 variable)	>1 million patients, >100,000 events from more than 30 countries	Treated kidney failure 2–5 years	0.88–0.91/+	+
KPNW[324, 326]	Age, sex, eGFR, albuminuria, systolic BP, antihypertensive use, diabetes, diabetes complications	39,013 patient, 1097 events from the Kaiser Permanente Health System (US)	Kidney failure 5 years	0.95/+	+
Landray et al.[327]	Sex, SCr, albuminuria, phosphate	595 patients, >190 events from the CRIB and East Kent cohorts in the UK	Kidney failure	0.91/+	-
Z6 Score[324]	SCr, albumin, cystatin C, urea, hemoglobin, ACR	7,978 patients, 870 events – Developed in the German CKD Study, validated in 3 additional European cohorts	Kidney failure 5 years	0.89–0.92/+	-

Table 20. Externally validated risk equations for predicting kidney failure in the general chronic kidney disease (CKD) (G3–G5) population. ACR, albumin-to-creatinine ration; CRIB, Chronic Renal Impairment in Birmingham; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; KPNW, Kaiser Permanente Northwest; SCr, serum creatinine; UK, United Kingdom; US, United States

We highlight here 3 validated models, The Kidney Failure Risk Equation (KFRE), the Veterans Affairs model, and the Z6 Score model. These all use routinely collected data from labs or electronic medical records and have been validated in different populations, both in North America and internationally to varying degrees. Detailed review of all existing prediction models is beyond the scope of this document.

The KFRE was developed and initially validated in 8391 adults from 2 Canadian provinces, and subsequently validated in 721,357 individuals from more than 30 countries spanning 4 continents.[9, 10] In this large validation study, cohorts from both general populations and nephrology clinic settings were included. Discrimination was excellent (C statistic >0.80 in 28/30 cohorts), and the use of a calibration factor improved calibration for some regions outside of North America; the validation populations now exceed 1 million individuals in more than 60 cohorts from nearly every continent.[323, 325] The KFRE is consistently highly accurate and has not been improved by addition of longitudinal slopes or variability of eGFR and urine ACR, or by adding cardiovascular comorbidities.[325]

A further 2 externally validated models from large US health systems (Kaiser Permanente North West and Veterans Affairs) also use routinely collected data and predict kidney failure with high accuracy within a 5-year horizon.[326, 328] Only one externally validated model for kidney failure has been developed using serum cystatin C (Z6 model), and although its highly accurate in 4 European cohorts, it has not been validated in other continents.[324]

The Work Group judged that the published externally validated models (delineated in Table 20) all had sufficient accuracy to be used in clinical settings. Given the potential benefits and utility of knowing the risk of kidney failure, patients and healthcare providers benefit should be encouraged to use these tools. Assessing risk of progression can aid in optimizing healthcare delivery services, facilitate the earlier identification of individuals for disease modifying therapy, help with planning for modality education, and identify goals of care planning. There are limited but supportive studies describing the better prediction of outcomes when using risk equations compared to care that is delivered according to isolated eGFR values and clinical judgement. Potential harms from the use of prediction equations could result from inappropriate use in settings of AKI or AKD or in younger individuals with CKD G1–G2 who may be at high risk of progression but low risk of kidney failure in the next 5 years. In these people, more proximal outcomes such as 40% decline in GFR or lifetime risk were judged to be more appropriate (that is establishing a validated risk equation for the appropriate outcome of interest, derived from the population of interest). As described above, healthcare providers should be cognizant of the impact of biological and analytical variability in albuminuria and eGFR values, and the subsequent impact on calculation of predicted risk of kidney failure.

Certainty of the evidence

To assess of the certainty of evidence, the ERT examined 2 existing systematic reviews[320, 329] addressing the question of the ability of risk prediction models to predict kidney failure (see Supplemental Table S14). The 2021 review from the NICE in the UK assessed the certainty of evidence for a variety of risk-based equations to predict kidney failure and concluded that there was high-quality evidence to state that the chosen risk prediction equations accurately predict kidney failure.[329] There was high certainty of the evidence (C-statistics were high and the confidence intervals were narrow). The Tangri 2013 review did not assess the certainty of evidence as part of the review (Supplementary Table S6).[320]

The Work Group agreed with the NICE assessment and considered evidence from other systematic reviews and recently published validation studies. The certainty of evidence was based on the established and growing evidence base for clinical validation and clinical utility as well as feasibility for validated risk prediction equations that predict kidney failure.

Values and preferences

The Work Group judged that accurate prediction of kidney failure was of importance to people with CKD, their families, and healthcare providers, and that most patients would choose to receive prognostic information about their individual risk of kidney failure as part of routine care. For a global guideline, the Work Group focused on prediction equations that were externally validated, had a low risk of bias, and included variables that were routinely available in most healthcare settings.

Resource use and costs

Most externally validated risk equations for predicting kidney failure use routinely collected data including laboratory variables such as eGFR, albuminuria, and serum albumin, phosphate, calcium, or hemoglobin, or information on demographics and comorbid conditions that can be easily obtained. As such, these models can be easily implemented at low cost to health systems. Only one externally validated model (Z6 Score) used cystatin C, and its usability in global health will depend on the potential increased routine availability of cystatin C in laboratories worldwide.

Considerations for implementation

Given the potential value of risk prediction models for planning and care decisions, healthcare providers should consider how to integrate risk prediction models into clinical practice, either in electronic medical records (EMRs), laboratory information systems, or using other mechanisms (mobile apps). These should aid clinical workflow and decision-making and even patient understanding. Where possible, laboratories should report the results from a validated risk equation specific to the region automatically for individuals with CKD G3–G5 when the required variables are available. Simpler equations can be implemented and reported when minimal data are available and more complex equations, requiring additional variables, can be implemented if the required data are present.

The reporting of risk in the laboratory reports and EMRs should be standardized with appropriate guidance on risk thresholds, when available. Local validation studies can be performed to determine optimal calibration of the specific risk prediction equations prior to implementation. Implementation of risk equations that are externally validated and use routinely collected data should be prioritized for health equity and global health considerations.

Rationale

Risk prediction equations that are externally validated, and locally calibrated, when possible, can lead to improvement in the delivery of CKD care. These equations should be used as they can further personalize care plans for people with CKD and enable discussions about the benefits and harms of disease modifying therapy.

This is a strong recommendation, as the workgroup judged that the evidence supporting both the clinical validity and clinical utility of risk prediction equations was sufficiently strong to recommend widespread adoption. The Work Group judged that most externally validated equations rely on routinely collected data and could therefore be implemented equally in low resource settings. The Work Group also judged that the majority of physicians will be comfortable in calculating the risk of kidney failure and discussing the risk and related treatment decisions with patients and caregivers.

Special considerations

Pediatric considerations

Work from the CKiD group (2015) provides a risk calculator for disease progression, using age, sex, glomerular vs. non-glomerular disease, eGFR, hypertension and laboratory parameters (calculator available at https://www.kidney.org/professionals/kdoqi/gfr_calculatorPedRiskCalc).[330] Further analyses combining the CKiD data with that from the ESCAPE trial (of BP control in CKD progression in children) resulted in a risk calculator which uses diagnosis, eGFR and proteinuria, and can be accessed at www.ckdprognosis.com.[331] The 4-value KFRE has been validated in the CKiD cohort with good discrimination.[332] However, further evaluation of the calibration in the cohort revealed incongruence between predicted and observed outcomes in those with higher predicted risks of kidney failure (who had lower observed risks).[333]

Considerations regarding sex and gender

There is uncertainty around whether sex assigned at birth or gender identity is to be used in risk equations. At present, a holistic approach should be utilized that takes into account sex assigned at birth, sex hormone milieu, and gender identity with shared decision-making with the person with CKD.

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.

In most developing and developed countries, there are insufficient nephrology care resources to manage all people with CKD. Using an objective tool to appropriately triage those most likely to benefit from referral may help to manage those nephrology resources in an evidence informed manner. Since only a small fraction of the CKD population is at high risk for progression to kidney failure, those people with lower risks of progression to kidney failure may be effectively managed in primary care settings with guideline-based treatments to delay CKD progression (Figure 12). Referral criteria for nephrology services that include a risk threshold of 3%–5% over 5 years have been examined retrospectively and have also been implemented prospectively in several health care settings.[334, 335]

In settings within Canada and the UK, retrospective studies have found that use of these risk thresholds has avoided harms from nonreferral or delayed referral of those progressing to kidney failure.[321] In addition, prospective evaluation has demonstrated a reduction in nephrology referral wait times, particularly for high-risk individuals. In other clinical settings with relatively scarce access to nephrology care, these thresholds should be adjusted to ensure wait times are acceptable for local standards.[335] Discussion of risk should also consider the individual person, their comorbidities, and their risk of death from other causes.

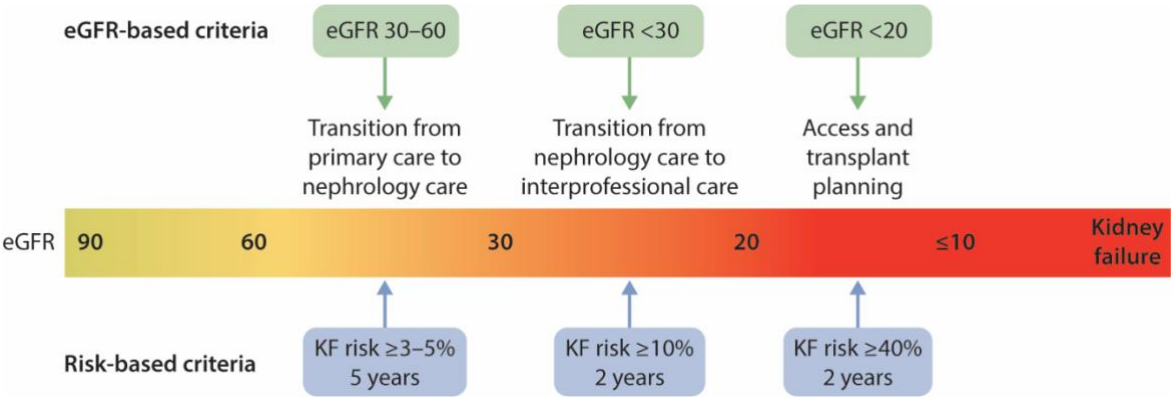


Figure 12. Transition from an estimated glomerular filtration rate (eGFR)-based to a risk-based approach to chronic kidney disease (CKD) care. KFRE, Kidney Failure Risk Equation

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.

Patients with CKD G4–G5 are more likely to develop concurrent complications of CKD including anemia, hyperkalemia, bone mineral disorders, and/or metabolic acidosis and protein-energy wasting. In addition, they remain at high risk for adverse events including AKI, emergency department visits, and hospitalizations. As such, in many countries and

healthcare settings, these patients may be enrolled in interdisciplinary care clinics or receive care management resources to reduce morbidity and healthcare costs, and to avoid unplanned dialysis initiation.

A risk threshold risk of >10% over 2 years has been studied and implemented in some jurisdictions in Canada as the key eligibility criteria for access to interdisciplinary care that includes a nurse, pharmacist, registered dietician or accredited nutrition provider, and other allied health support. This practice point is based on results from these studies, which demonstrate acceptance and preference of a risk-based criteria by patients and providers.[336] Given the costs associated with delivery of care management resources and interdisciplinary models, risk-based thresholds offer a useful guide to the selection of the ideal target patient population to derive the most benefit from the highly specialized team.

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.

The appropriate timing for modality education, timing of vascular access planning, or referral for transplantation in a patient with low or declining GFR can be difficult to predict. Vascular access planning in all adults with CKD G4 would lead to the unnecessary placement of fistulae, whereas waiting until eGFR falls below 15 ml/min per 1.73 m^2 may lead to inappropriate overuse of central venous catheters at dialysis initiation. Studies have described the potential utility of risk-based thresholds in planning for dialysis access specifically and found acceptable specificity and positive predictive values for the risk-based threshold criteria as compared with eGFR alone. The Work Group noted that the KDOQI vascular access guideline (2019) currently recommend a risk-based threshold >50% or eGFR <15 ml/min per 1.73 m^2 for initiation of vascular access planning, while acknowledging that access to surgeons and primary failure to maturation rates may vary by patient and by center.[337] Based on current evidence, a threshold of >40% risk or eGFR 15 ml/min per 1.73 m^2 are acceptable to use for initiating vascular access referral.

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

The Work Group recognizes that progression of CKD can occur at all severities, and that in earlier stages of disease (G1–G3), large declines in eGFR can occur in 2- to 5-year timeframes without reaching kidney failure (Figure 13).

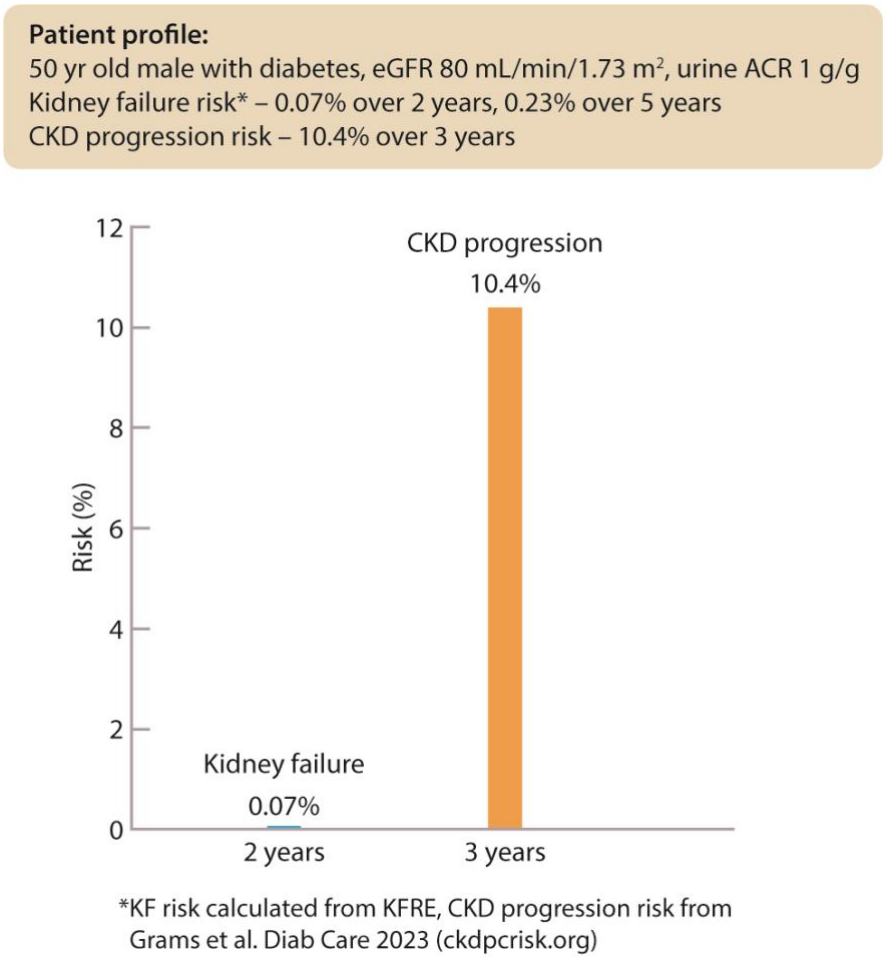


Figure 13. Comparison of risk of chronic kidney disease (CKD) progression (40% decline) vs. kidney failure in adults with CKD G1–G2. *Kidney failure risk calculated from KFRE, CKD Progression risk from Grams et al. Diab Care 2023 (ckdpcrisk.org)

Risk prediction models developed in populations with later stages of CKD are not accurate in CKD G1–G2, whereas alternative, accurate, externally validated risk prediction equations have been developed for predicting 40% decline in eGFR or kidney failure at all stages of CKD. For this intermediate CKD progression outcome, 3 recent publications present models for patients with or without diabetes, using both regression and machine learning-based methods, with or without biomarkers (Table 21).[8, 338, 339] Given the potential utility of these new models to identify high-risk people for early intervention, they should be used to predict disease progression in people with CKD G1–G2 and may supplement established risk equations among patients with CKD G3.

	Variables	Population/Events	Time horizon	Discrimination and calibration
CKD-PC[339]	16 variables including	1.6 million adults with or at risk for CKD	5 years	0.74–0.77
Klinrisk[8]	20 laboratory variables derived from CBC, chemistry panel and urine	177,196 adults with CKD G1–G4 or at risk for CKD	1–5 years	0.84–0.88
KidneyIntelx[338]	3 proprietary biomarkers, 5 additional clinical variables including albuminuria, BP	1146 adults with CKD (G1–G3) and diabetes	5 years	0.77

Table 21. Externally validate risk equations for predicting 40% decline in GFR. CBC, complete blood count; CKD, chronic kidney disease; CKD-PC, Chronic Kidney Disease Prognosis Consortium

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

Risk prediction models for specific etiologies of CKD have also been developed, are externally validated, and used in healthcare settings to guide clinical care. For autosomal dominant polycystic kidney disease (ADPKD), 2 equations can be useful in determining the longer term risk of kidney failure and may guide therapy with tolvaptan - the Mayo Clinic Classification tool and the Predicting Renal Outcome in Polycystic Kidney Disease (ProPKD) score,[340, 341] which incorporates genetic data. Of these, the Mayo Clinic Classification tool has been shown to be accurate in external validation.

In patients with IgAN, 2 externally validated prediction tools (clinical or clinical + histology) have been developed using large international cohort studies. Models that included the mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T) (MEST) histological score were more accurate (C statistic 0.81–0.82 vs. 0.78) and showed improved reclassification in development and external validation datasets.[342, 343] Given the availability of accurate externally validated models, these should be preferentially used over more general CKD models in people with an established diagnosis of IgAN or ADPKD.

2.3. 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 models that are either developed within CKD populations or that incorporate eGFR and albuminuria.

Cardiovascular morbidity and mortality disproportionately affect people with CKD, and risk prediction tools developed in the general (non-CKD) population may underestimate the risk of atherosclerotic cardiovascular disease (ASCVD) or heart failure in CKD populations. Absolute risk is used to determine eligibility for disease-modifying

pharmacological therapy in cardiovascular disease guidelines, and underestimation of risk may lead to suboptimal treatment of people with CKD, perpetuating biases ("renalism") that have existed for more than 2 decades. New models that have been developed specifically in adults with CKD (QRISK3[44]) and modifications to existing cardiovascular disease (CVD) models (pooled cohort equations [PCE]/ Systematic COronary Risk Evaluation [SCORE] [45]) that include eGFR and albuminuria should be used to predict cardiovascular events in individuals with CKD. [344, 345] [344, 345] [341, 342] [378, 379] [378, 379] [379, 380] [379, 380] [382, 383] [382, 383] [382, 383] [382, 383] [382, 383] [379, 380] [379, 380] [381, 382] [381, 382] [286, 287] [270, 271] [270, 271] [270, 271] [270, 271] [270, 271] [87, 88] [84, 85] [84, 85] [63, 64] In the case of the PCE, the CKD patch significantly improves calibration of ASCVD risk, and the eGFR patch improves prediction of CVD mortality using SCORE.

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

Patients with CKD are at high risk of all-cause mortality, and the competing risk of death can affect clinical decision-making, particularly for older adults with CKD G4, who may simultaneously be at high risk of kidney failure requiring dialysis. All-cause mortality can be challenging to predict due to the multiple biological pathways, and differences in personal preferences and goals of care that are not captured by risk prediction models. Models developed by the CKD-PC for multiple outcomes in CKD G4+ predict the risk of death, non-fatal CVD event, or kidney failure in adults at 2 and 4 years.[6, 346] A 5-year mortality model was also developed in the Cardiovascular Health Study, where the majority of people had CKD G3.[346] Both models have modest discrimination (C statistics ~ 0.70). These may be more appropriate to identify high-risk groups, where earlier discussions about conservative care pathways or alternative goals of care may have been helpful. These models should not be used to determine the futility of initiating KRT.

CHAPTER 3. DELAYING CKD PROGRESSION AND MANAGING ITS COMPLICATIONS

3.1. CKD treatment and risk modification

Practice Point 3.1: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications (Figure 14).

Risk factors associated with CKD progression, CVD, and other CKD complications are highly interrelated,[347] and hence so is their management. We use the term "CKD treatment and risk modification" to encompass the aim of CKD treatment, which is to impart meaningful beneficial effects on "CKD manifestations" and on "CKD outcomes" (Figure 14). CKD manifestations include symptoms and clinical/laboratory abnormalities associated with CKD which confer health implications. These include increased BP, anemia, dyslipidemia, CKD-mineral and bone disorder (CKD-MBD), potassium disorders, severe acidosis, decreased fertility, and increased risk of complications of pregnancy. CKD outcomes refer to progression to kidney failure and CKD-associated morbidity and mortality. These are wide ranging and include several cardiovascular diseases, hospitalization, infections, gout, etc. Reducing the risk of CKD progression by targeting its underlying pathophysiology may have beneficial effects on a range of CKD manifestations and CKD-associated outcomes, whilst some complications may need specific targeted interventions. Healthcare systems should aim to provide safe and proven cost-effective therapies which achieve CKD treatment and risk modification and to minimize limitations to access for people with CKD as their disease can substantially impact on quality of life and healthcare system resources. A key goal for healthcare providers should be to identify people at risk and to start such treatments early in the course of CKD in order to maximize potential benefits.

Fertility

CKD is associated with decreased female and male fertility.[348, 349] Progressively impaired function of the hypothalamic-pituitary-gonadal axis appears to play a key role in the pathophysiology, although multiple factors contribute to the reduction in fertility in this population. In conjunction with the decreased fertility associated in CKD and the uncertainty of the impact of assisted reproductive technologies on kidney function, ongoing discussion of family planning potential between the person with CKD and their healthcare provider is essential.

Pregnancy

People with CKD are at risk for adverse pregnancy-associated outcomes, including progression of their underlying CKD, a flare of their kidney disease, and adverse pregnancy complications including preeclampsia, preterm delivery,[350, 351] and small for gestational age infant. The severity of CKD is associated with risk of adverse pregnancy outcomes. A multidisciplinary approach to preconception counselling and management of pregnancy is necessary to achieve optimal outcomes for both the person with CKD and the infant.[352]

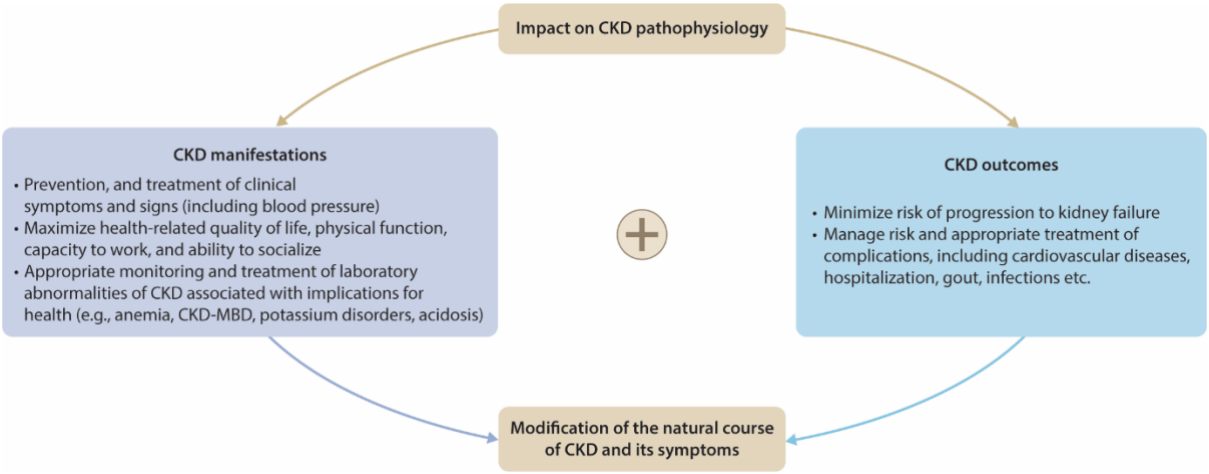


Figure 14. Chronic kidney disease (CKD) treatment and risk modification. CKD-MBD, chronic kidney disease-mineral and bone disorders

This chapter provides evidence-based guidelines to support holistic management of the risks associated with CKD (Figure 15). Previously published KDIGO clinical practice guidelines for the management of BP, diabetes, lipids, anemia, and CKD-MBD in CKD are available and support our statements.[15-17, 19, 59] This chapter also describes certain laboratory abnormalities including bicarbonate, potassium, and uric acid; together with a summary of the observed ranges associated with different stages of CKD.

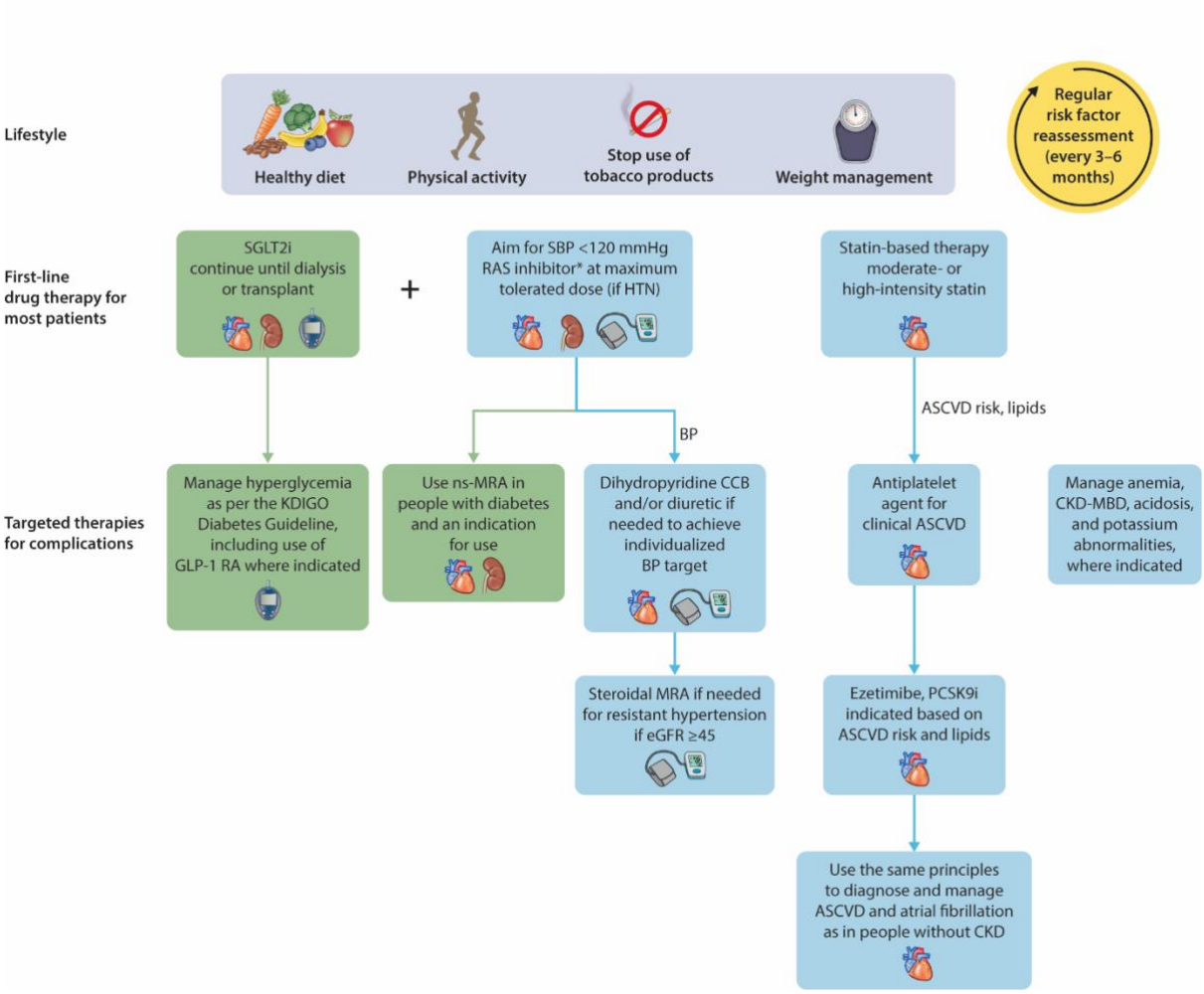


Figure 15. Holistic approach to chronic kidney disease (CKD) treatment and risk modification.
*Angiotensin-converting ezyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all 3 classes are often needed to attain blood pressure (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; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor

3.2. 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, dieticians, physical and occupational therapy, and smoking cessation programs) should be offered where indicated and available.

This practice point calls out the need for a comprehensive and integrated approach to lifestyle modification and recognizes that in some circumstances there is value in referring

people to professionals or programs with expertise in lifestyle modification. We also appreciate that different healthcare systems and regions will have variable access to such specialized services or teams, and thus availability may be an issue.

3.2.1. Avoiding use of tobacco products

The Work Group concurs with the previous KDIGO recommendations to advise patients with diabetes and CKD who use tobacco to quit using tobacco products[19] and extends that advice to all people with CKD who use tobacco products to reduce risk of associated premature mortality from CVD, as well as risk of respiratory diseases and cancer.[353] Intensive nurse-led programs appear effective at supporting smoking abstinence, and can be combined with pharmacological intervention (e.g., nicotine replacement therapy of nicotine-receptor partial agonists) to improve smoking abstinence over 16 weeks.[354] See the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD* and *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* for full details.[17, 19]

3.2.2. Physical activity and optimum weight

The 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*[19] and consider that they should extend to all adults with CKD. We draw attention to the following statements.

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

Practice Point 3.2.2.3: People with CKD should be advised to avoid sedentary behavior.

Practice Point 3.2.2.4: 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 3.2.2.5: Physicians should consider advising/encouraging people with obesity and CKD to lose weight, particularly people with eGFR ≥30 ml/min per 1.73 m^2.

BMI relates to levels of adiposity on a population scale (though imperfectly) and a BMI over 25 kg/m^2 in adults (i.e., overweight or obese) is associated with an increased risk of multiple chronic diseases including development of CKD.[355, 356] Such adiposity-CKD associations appear to be causal.[357, 358] BMI can overestimate risk in people with high muscle

mass,[359] and risk for a given BMI may vary by ethnicity (with Asians being at higher risk of metabolic disorders at lower BMIs than Europeans).[359, 360] It is important to provide people with CKD advice about their weight using BMI in conjunction with other information, including ethnicity, diet, comorbidity, physical activity levels, risk of falls, and laboratory values.

Special considerations

Pediatric considerations

Practice Point 3.2.2.6: 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.

The WHO recommends 60 minutes of moderate-to-vigorous physical activity daily for children 5–17 years old, including aerobic activities as well as activities that strengthen muscle and bone.[361] Limits on sedentary time, particularly screen time are also recommended. For children 1–5 years of age, 180 minutes per day of physical activity is recommended; young children in this age group should not be restrained (i.e., in a stroller or carrier) for >60 minutes at a time. Only 13.4% of 224 participants of the CKiD study aged ≥12 years old (median [IQR]: 15 years) met these WHO targets,[160, 177, 220, 221, 362] compared with 25% of general population children of comparable age.[363] Less than 2% of CKiD participants met screen time recommendations (<2 hours per day on school days), compared with 27% of the general population. Physical activity has numerous benefits for cardiovascular, mental, and social health. Given that children with CKD are at higher risk for problems in all these areas, physical activity may be even more important in the CKD population.

3.3. 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 registered dieticians or accredited nutrition providers to provide information for 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, where available.

A whole-food, plant-based diet low in animal protein and ultra-processed foods may be helpful to slow the progression of CKD and delay need for dialysis via reduction of cardiometabolic risk factors such as hypertension, CVD, diabetes, and obesity.[364, 365] Ultra-processed foods such as sugar-sweetened beverages, fast foods, frozen meals, chips, candy, and pastries are high in salt, sugar, and fat, and low in nutritional value, promote inflammation which may contribute to worsening kidney function. A plant-based diet is rich in anti-inflammatory nutrients, fiber, and phytochemicals and has been shown to reduce proteinuria and decrease metabolic acidosis.[364, 365] The probiotic nature of plant-based foods

may also support the microbiome and reduce inflammation and intestinal production of uremic toxins.[366] A recent systematic review evaluated the association of dietary patterns and kidney-related outcomes.[367, 368] Dietary patterns which include more plant-based unprocessed protein have been demonstrated, in cohort studies and small RCTs, to slow the trajectory of eGFR decline, reduce the risk of kidney failure, reduce risk of mortality, and improved scores in some quality of life domains (e.g., Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diet).

3.3.1. Protein intake

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

This recommendation places a higher value on slowing the rate of GFR decline without the challenges associated with adherence to lower-protein diets, potential adverse effects, and the contraindications in people with sarcopenia, cachexia, or undernutrition. The group judged that many well-informed people with CKD G3–G5 would choose to implement this recommendation. .

Key information

Balance of benefits and harms

The Work Group considered it safe to restrict protein intake to 0.8 kg/g day in adults unless it is contraindicated or KRT is initiated. Restricting protein may adversely impact quality of life (QoL) altering fundamental components of a person's culture and daily life. Adherence to low-protein diets long-term is challenging. Thus, considerations for degree of protein restriction in the context of individual preferences, true impact on CKD progression based on etiology, and other factors need to be considered. There is little evidence to support protein restriction with the goal of preventing progressive loss of kidney function, need for KRT, and cardiovascular mortality, and benefits should be weighed against risk for malnutrition

The protein type, not only the quantity, may also be relevant. In a recent systematic review, Wong *et al*. (in development) evaluated type of protein intake with kidney-related outcomes. The studies reviewed include small RCTs using soy- or other vegetable-based protein diets with ketoanalogues compared to animal-based protein diets in those with or with diabetes and showed variable outcomes with respect to changes in eGFR over time; none assessed kidney failure nor measures of patient preferences. Table 22 briefly summarizes the impact of plant-based protein diets in people with CKD. In another cohort study of older subjects (N=291, mean age 76) with eGFR <60, there was no significant association between vegetable protein intake and change in eGFR.[369]

Study N Study design	CKD stage or GFR	Intervention Follow-up	Outcome
CRIC[370] N=2403 Observational	20–70 ml/min per 1.73 m^2	High DASH vs. low DASH 14 year	CKD progression: HR: 0.83; 95% CI: 0.69–0.99 Mortality: HR: 0.75; 95% CI: 0.62–0.90
NHANES[371] N=1110 Observational	30–59 ml/min per 1.73 m^2	DASH by quintiles 7.8 year	Kidney failure relative hazard (RH) compared to Quintile 5: Quintile 1: RH: 1.7; 95% CI: 1.1–2.7; Quintile 2: RH: 2.2; 95% CI: 1.1–4.1
CORDIOPREV[372] N=53 RCT	<60 ml/min per 1.73 m^2	Mediterranean diet vs. low-fat diet 5 year	Decline in GFR -3.72 ml/min per 1.73 m^2 vs. -5.4 ml/min per 1.73 m^2, p=0.03
CKD.QLD[373] N=145 Observational	CKD G3–G4	High vegetable and nut intake Median 36 month	Composite all-cause mortality, kidney failure, or doubling of SCr: HR: 0.61, 95% CI: 0.39–0.94
REGARDS[374] N=3972 Observational	<60 ml/min per 1.73 m^2	Plant-based diet 6 year	All-cause mortality: HR: 0.77; 95% CI: 0.61–0.97
NHANES III[375] N=5,346 Observational	<60 ml/min per 1.73 m^2	Increasing plant-to-protein ratio 8.4 year	All-cause mortality for every 33% increase: HR: 0.77, 95% CI 0.61–0.96
Longitudinal Study of Aging Women[376] N=1374 Observational	Baseline 65.6 ± 13.1 ml/min per 1.73 m^2	Higher vs. lower intake of plant-based protein 10 year	Each 10 g higher intake of plant-based protein reduced decline in GFR by 0.12 ml/min per 1.73 m^2/year

Table 22. Impact of plant-based protein in people with chronic kidney disease (CKD). CI, confidence interval; CKD QLD, Chronic Kidney Disease in Queensland; CORDIOPREV, CORonary Diet Intervention with Olive oil and cardiovascular PREVention study; CRIC, Chronic Renal Insufficiency Cohort; DASH, Dietary Approaches to Stop Hypertension; GFR, glomerular filtration rate; HR, hazard ratio; NHANES, ;RCT, randomized controlled trial; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SCr, serum creatinine

Certainty of evidence

The certainty of evidence was moderate that there was little to no difference in the critical outcome all cause death and kidney failure prevention when comparing very low-protein to low- or normal-protein diets, and moderate that there was some benefit to the critical outcome of kidney failure for the comparison of very-low protein diets to low- or normal-protein diets as demonstrated by the wide CIs for these outcomes including potential for important benefits and harms. In addition, there was important and unexplained heterogeneity present. It is uncertain whether low- or very low-protein diets impact change in GFR.

The certainty of evidence was very low when comparing low- protein to normal-protein diets for change in GFR and low when comparing very low-protein to low- or normal-protein diets. This is because the confidence intervals included potential for important benefits and harms, there was important and unexplained heterogeneity present, the outcome was reported as a surrogate outcome, and there was unclear allocation concealment in 4 studies.

The overall certainty of evidence for the remaining outcomes was very low because of increased risk of bias and small studies with wide confidence intervals. Also, no studies addressed the critical outcome of progression to kidney failure. In addition, many studies were unclear about allocation concealment/random sequence generation, had significant, unexplained heterogeneity, wide confidence intervals for important benefits and harms, and use of surrogate outcomes.

Value and preferences

The Work Group judged that some clinically suitable people would choose to implement a diet with protein restriction to 0.8 g/kg/d unless there are conditions that contraindicate such as sarcopenia, cachexia, or undernutrition. Additionally, the Work Group judged that protein restriction would be implemented by many people as a way of managing their kidney disease. It will also have an impact on overall QoL with the adoption of a more plant-based diet; however, there may be challenges with implementing and adhering to these changes.

Resource use and costs

The risks, benefits, resource use, and costs of protein restriction should be considered when treating people with CKD. The Work Group considered that plant-based proteins could have a cost-benefit effect compared to animal-based protein but evidence in this topic remains limited.

Considerations for implementation

Consider the use of culturally appropriate foods that are more familiar to people, and consider nutritional status, goals of care, and QoL in recommendations which would restrict choices for people with CKD.

Rationale

The Work Group suggests modest protein restriction based on consideration of the possible benefits of kidney protection and if implemented with appropriate supervision and expertise, the possible benefits may outweigh the potential adverse effects. People with CKD not on dialysis with or without diabetes may opt for some degree of protein restriction, especially as control of dietary intake empowers people with CKD and supports self-management. People put a large value on diet, cultural preferences, and QoL; however, adherence to a low-protein diet remains challenging, may impact social and psychological well-being, and given that most of the trials for protein restriction were conducted before RASi and SGLT2i were implemented, may not be worth the sacrifice/change in lifestyle. The impact of protein restriction and use of non-animal-based protein diets should be evaluated in the context of new care paradigms to ascertain the incremental gain of these strategies relative to the efforts and costs.

Practice Point 3.3.1.1: Do not restrict protein intake in adults with sarcopenia, cachexia, or conditions that result in undernutrition.

Depending on the region of the world, 11%–50% of adults and 20%–45% of children with CKD have malnutrition characterized by protein-energy wasting (PEW).[377] The risk increases as CKD progresses to later stages and is also influenced by comorbid conditions such as diabetes, autoimmune diseases, and CVD. PEW is multifactorial, driven in part by the negative impact of uremic toxins on appetite and chronic inflammation. Given these data and the negative impact on prognosis and QoL, nutritional screening and intervention by an accredited nutrition provider for all people with CKD that present with frailty, weight loss, poor growth (pediatrics), or poor appetite, and all people with CKD G4–G5 is advised.

Under adequate supervision and patient education, low-protein diets have not led to malnutrition risk.[377-379] However, malnutrition risks can be theoretically exacerbated by a low-protein diet in people with conditions linked to sarcopenia and cachexia, such as frailty. Note that statements about reduction in dietary protein do not apply to pediatric populations given issues related to growth and nutrition.

Practice Point 3.3.1.2: Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.

There is some evidence to suggest that higher protein diets above the recommended daily intake may accelerate kidney functional decline in people with CKD G1–G3. In a study of 1624 women enrolled in the Nurses′ Health Study, the effect of protein intake over an 11-year period in women with eGFR ≥80 ml/min per 1.73 m^2 (normal GFR) at baseline and those with eGFR 55–80 ml/min per 1.73 m^2 measured the impact of dietary protein intake measured twice during the study period at intervals of 4 years using a semiquantitative food-frequency questionnaire.[380] While those women with normal GFR did not display any adverse effects of high protein intake, they did demonstrate a significantly faster change in

eGFR in relation to protein intake The effect was greatest in those with the highest intake of non-dairy animal protein.

Special considerations

Pediatric considerations

Practice Point 3.3.1.3: 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.

Children with CKD likely have similar resting energy expenditure to healthy children and should have total energy requirements in the normal range.[381] As in adults, protein restriction was considered for children with CKD in the past. Two RCTs have compared low-protein versus normal-protein diets in children with CKD.[382, 383] One found poorer growth for those on a low-protein diet and the other found no difference in eGFR between the groups. A 2007 Cochrane meta-analysis concluded there was uncertainty over the possible harm of strict low-protein diets on growth in young infants.[384] The 2009 KDOQI guidelines and the 2020 Pediatric Renal Nutrition Taskforce suggest maintaining an intake of dietary protein at 100%–140% of the dietary reference intake (DRI) or the SDI for ideal body weight in children with CKD G3 and at 100%–120% of the DRI/SDI in children with CKD G4–G5.[385, 386]

3.3.2. Sodium intake

The Work Group concurs with the following recommendation from *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*[19] and the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD.*[17]

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 not appropriate for patients with sodium-wasting nephropathy.

Global average sodium intake is estimated to be 4310 mg/day (10.78 g of salt per day), which far exceeds the physiological requirement and is more than double the WHO recommendation of <2 g of sodium (equivalent to <5 g of salt) per day in adults.[387] There are large-scale RCTs quantifying the benefits of restricted salt intake (e.g., using 75% sodium and 25% potassium chloride salt substitutes) to lower BP and reduce risk of cardiovascular events in the general population.[388] In RCTs with up to 36 weeks of follow-up, reduction in dietary sodium has also been shown to lower BP and levels of albuminuria in people with CKD.[388-391] Although presumed to reduce risk of CKD progression and CVD, longer term trials have not been conducted to confirm these effects translate into reduced risk of clinical

outcomes in CKD.[389] Given the effects of sodium restriction on BP, it is reasonable to recommend sodium restriction to people with CKD in combination with pharmacological strategies to minimize the risk of kidney and cardiovascular diseases. Rarely, people with CKD may have salt-wasting kidney disease in which case this recommendation may not apply.

Special considerations

Pediatric considerations

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

The WHO recommends that the maximum intake of <2 g/day sodium (<5g/day salt) in adults should be adjusted downward based on the energy requirements of children relative to those of adults (Table 23). Children born with low birth weight (<2.5 kg) are at increased risk for CKD in later life and may also be at higher risk for hypertension and increased salt-sensitivity. Salt-sensitivity is a physiological trait by which blood pressure in some people exhibits changes parallel to changes in salt intake. Children born with low birth weight may have a 37% increased salt sensitivity (defined as an increase in mean BP ≥3 mm Hg over 24 hours while on a high salt diet, when compared with a controlled salt diet). That sensitivity may increase further in those who are small for gestational age.[392]

Age	Recommended adequate sodium intake (g/day)
0–6 months	0.110
7–12 months	0.370
1–3 years	0.370
4–8 years	1.0
9–13 years	1.2
14–70 years	1.5

Table 23. Age-based sodium intake recommendations[391]

Children with CKD often have underlying tubular conditions that predispose them to numerous electrolyte losses, including sodium. For these children a supplemented rather than restricted sodium intake will be required. For non-salt wasting children, salt intake should be limited to the age-based Recommended Daily Intake.

3.4. Blood pressure control

The Work Group concurs with the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD* which encourages individualized BP targets and use of agents according to age, coexistent CVD, and other comorbidities; risk of progression of CKD; and tolerance to treatments.[17] 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.

An observational study demonstrated that on average, each 20 mm Hg higher usual SBP and 10 mm Hg higher DBP is associated with an approximate doubling of cardiovascular risk, with no lower limit down to at least 115/75 mm Hg.[393] Data from the Systolic Blood Pressure Intervention Trial (SPRINT) support a target SBP of <120 mm Hg (when measured using a standardized office BP measurement) to reduce cardiovascular risk in adults aged >75 years, or aged >50 years with one or more of the following risk factors: clinical or subclinical CVD (other than stroke); eGFR 20–60 ml/min per 1.73 m^2; or ≥15% 10-year cardiovascular risk.[394] Compared to a target of 140 mm Hg, this approach reduces risk of major adverse cardiovascular events (MACE) by one-quarter (hazard ratio [HR]: 0.75; 95% CI: 0.64–0.89). That relative benefit was similar in people with and without CKD. The SPRINT trial excluded people with diabetes, but cardiovascular benefits of intensive BP lowering on risk of stroke and heart failure are clearly apparent in people with diabetes in individual patient level data meta-analysis of intensive versus standard BP-lowering trials.[395]

Standardized BP monitoring can be challenging to offer in a clinic setting due to the time required,[396] however it is considered potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a nonstandardized manner.[396] A practical solution to ensure high BP is identified is by using home-based monitoring (or telemonitoring). Trials have shown that 2 morning and evening BP measurements taken during the first week of every month can be used to titrate antihypertensive medication and reduce BP more than "usual care" approaches.[397]

People who are frail, have limited life expectancy, or have a history of falls may have increased risk of additional events if BP targets of <120 are achieved. Postural hypotension in these people is associated with adverse outcomes, and thus weighing the benefits of some attenuation of eGFR decline versus the life-changing impact of falls, fractures, and other events should be considered in choosing specific targets.

Special considerations

Pediatric considerations

The Work Group concurs with the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD* and we highlight the following guidance:[17]

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: We suggest monitoring BP once a year with ABPM and monitoring 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.

These statements with respect to children are generally worded to maintain consistency with the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD*,[17] where the full rationale and evidence behind the statements is available. However, the suggestion to target auscultatory office SBP at <50th percentile when ABPM is not available departs from the BP guideline (the previous guideline suggested a target <90th percentile). While office BP may be higher than BP measured by ABPM, this is not universally the case. Given the evidence that intensive BP control may slow CKD progression together with the very low risk of adverse effects of intensive BP lowering in children,[151] we consider that more intensive BP lowering targeting around the 50th percentile is reasonable. However, a target even lower than the 50th percentile has not been shown to offer additional benefits. Recent trial data found using a target of office auscultatory SBP at 50th to 75th percentile versus intensive control to below the 40th percentile did not result in significant differences in left ventricular mass index.[152]

3.5. Renin-angiotensin system inhibitors

The Work Group highlights recommendations from the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD* and selected practice points for treatment with RASi from the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD*[17] and the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD.*[19] These include:

Recommendation 3.5.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes (1B).

Recommendation 3.5.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (2C).

Recommendation 3.5.3: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).

Recommendation 3.5.4: 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 3.5.1: 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 3.5.2: 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 3.5.3: 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 3.5.4: 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 3.5.5: 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 3.5.6: Consider starting people with CKD with mildly increased albuminuria (A1) with RASi (ACEi or ARB) for specific indications (e.g., to treat hypertension or heart failure with low ejection fraction).

The role of RASi in the management of BP and people with CKD, diabetes, and/or high BP have been specifically considered in recent KDIGO guidelines.[17, 19] Although temporarily stopping RASi may be a valid treatment strategy for emergent hyperkalemia, we recommend to ensure reinitiation of treatments once the adverse event is resolved, so that patients are not deprived of a needed medication (Practice Point 4.3.3).[398-402] The Work Group offer a new practice point and a revised algorithm for initiation of RASi (Figure 16).[19] The algorithm has been updated to suggest a ≥30% decrease in eGFR (rather than increase in creatinine) should be a trigger to investigate for an underlying other condition. This represents a threshold above which the eGFR change is greater than would be expected from natural variation.

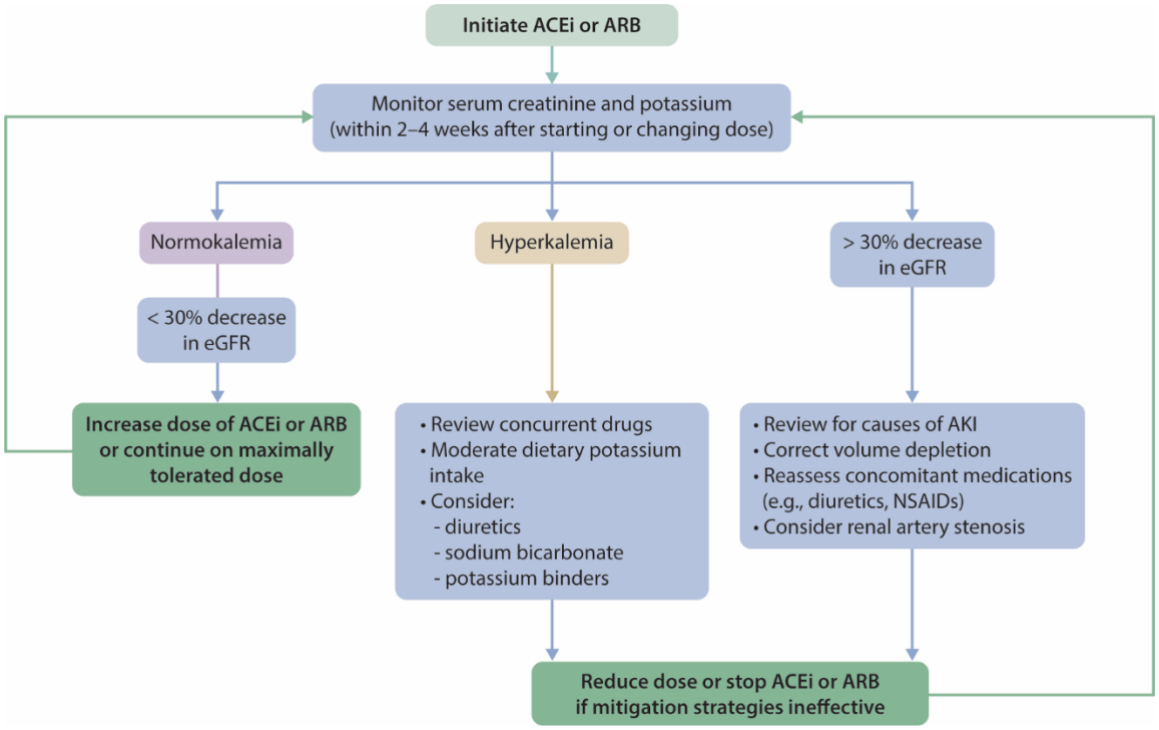


Figure 16. Algorithm for monitoring of potassium and glomerular filtration rate (GFR) after initiation of renin-angiotensin system inhibitors (RASi). ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

Practice Point 3.5.7: Continue ACEi or ARB in people with CKD even when the eGFR falls below 30 ml/min per 1.73 m^2.

In a recent STOP-ACE trial of 411 participants with mean eGFR of 13 ml/min per 1.73 m^2, a policy of discontinuing RASi in CKD G4–G5 did not result in any kidney or cardiovascular benefits.[403] Two observational studies have also found associations suggesting outcomes were worse among participants who stopped RASi after an episode of

hyperkalemia or acute kidney injury (AKI), with an eGFR <30 ml/min per 1.73 m^2, compared with those that continue.[404, 405]

3.6. Sodium--glucose contransporter-2 inhibitors (SGLT2i)

The Work Group concurs with the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD* which stated: "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)*.[19] However, in these guidelines, we offer a more general 1A recommendation for adults with CKD. We also highlight practice points from the KDIGO Diabetes guideline for diabetes management in CKD which are also relevant for people with CKD without diabetes:

Recommendation 3.6.1: 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 3.6.1: 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 3.6.2: 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 3.6.2: We recommend treating adults with CKD and heart failure or eGFR ≥20 ml/min per 1.73 m^2 with urine albumin-to-creatinine ratio (ACR) ≥200 mg/g with an SGLT2i (1A).

Practice Point 3.6.3: 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.

Use of SGLT2i in people with T2D is recommended in previous guidelines irrespective of level of albuminuria. This new recommendation places high value on the importance of reducing risk of kidney failure, cardiovascular mortality, and heart failure in people with CKD and high value on the large relative reductions in risk for kidney disease progression in a series of large, placebo controlled RCTs. It also places moderate value on the benefits of SGLT2i on risk of AKI, cardiovascular death, hospitalization for heart failure and myocardial infarction, risk of hospitalization from any cause, and high value on the demonstrable net absolute benefits versus absolute harms in people with CKD (particularly in those without diabetes who are at very low risk of ketoacidosis). SGLT2i also favorably reduce BP, uric acid levels, measures of fluid overload, the risk of serious hyperkalemia, and do not increase risk of hypoglycemia. The recommendation is consistent with but expands on Recommendation 1.3.1 from the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD to include people with causes of CKD not related to diabetes.

Key information

Balance of benefits and harms

Benefits

Several large, placebo-controlled RCTs have provided clear demonstrations of the efficacy of SGLT2i, which substantially reduce risk of kidney failure, AKI, hospitalization for heart failure as well as moderately reduce the risk of cardiovascular death and myocardial infarction in people with and without CKD. These benefits appear to be irrespective of diabetes status, cause of kidney disease, or level of GFR.[406, 407] The benefits of SGLT2i in the people with diabetes and CKD have been fully described in the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*.[19]

Two large RCTs using 2 different SGLT2i recruited 10,913 participants and focused on CKD populations at risk of progression, reporting benefits in terms of kidney disease progression.[317, 408] Key differences between the 2 trials were the inclusion of a large number of causes of kidney disease not related to diabetes, lower eGFR, and lower levels of ACR in The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) compared to the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.

In a collaborative metanalysis including those 2 and 11 other trials (13 trials with just over 90,000 randomized participants) in comparison to placebo, those allocated to an SGLT2i experienced a 37% reduction in the risk of kidney disease progression and a 23% reduction in the risk of AKI irrespective of diabetes status (Figure 17).[406]

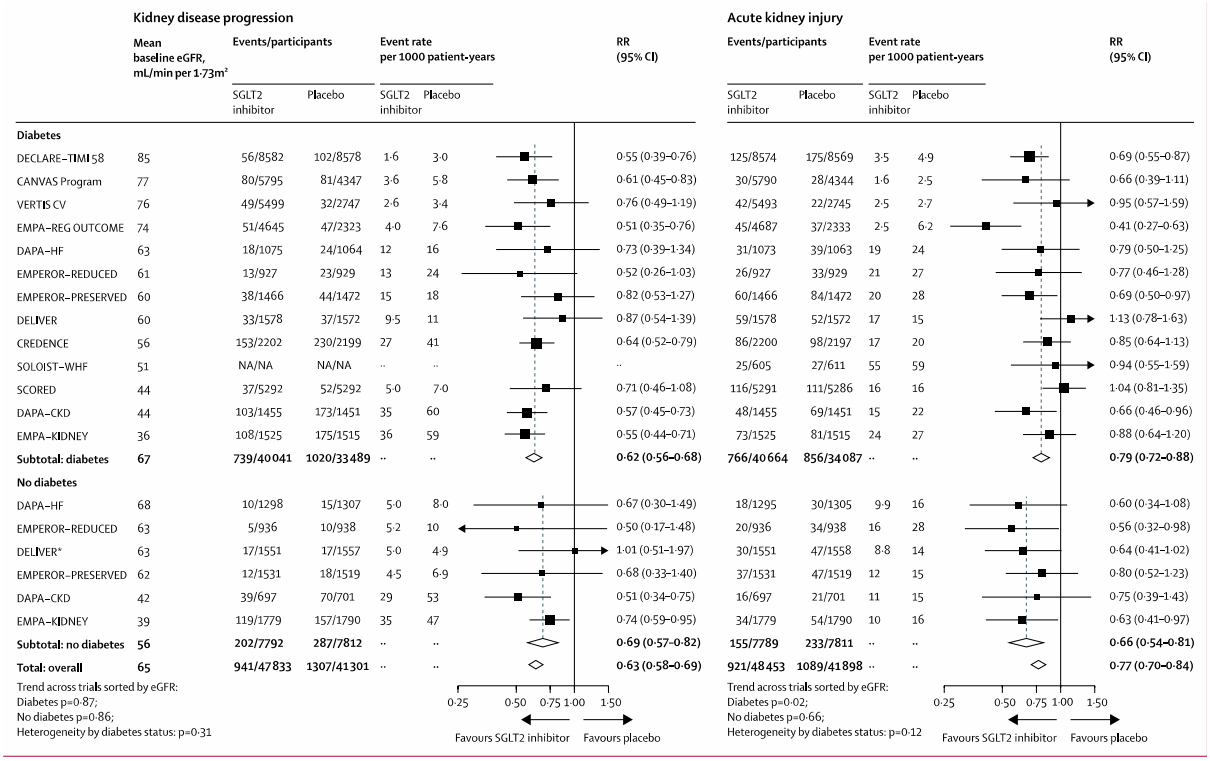


Figure 17. Effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) with kidney disease outcomes by diabetes status. CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk. Reproduced from Nuffield Department of Public Health (NDPH) Renal Studies Group and SMART-C Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet Figure 1.[406]

The same meta-analysis showed that, compared with placebo, allocation to an SGLT2i reduced the risk of the composite of cardiovascular death or hospitalization for heart failure by 23% irrespective of diabetes status (Figure 18), although there were limited numbers of cardiovascular events in people with CKD without diabetes. SGLT2i also afford an approximate 10% relative risk reduction in major adverse cardiovascular events (MACE), primarily from reduced risk of cardiovascular death and myocardial infarction with no clear effect on stroke.[406, 407]

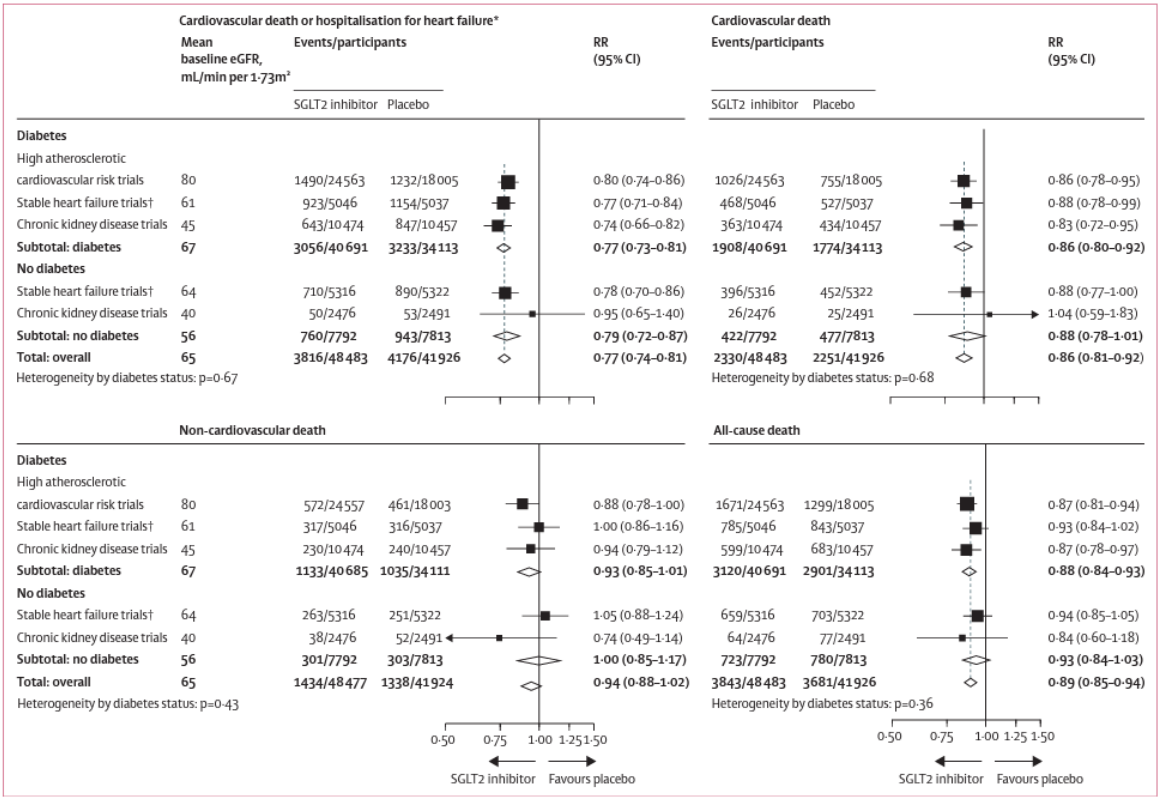


Figure 18. Effects of sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibition versus placebo on cardiovascular and mortality outcomes by diabetes status and trial population. CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk. Collaborative meta-analysis of data from 13 large placebo control trials of SGLT2 inhibitors. Reproduced from Renal Studies Group and SMART-C Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet Figure 3.[406]

Furthermore, SGLT2i also importantly reduce risk of hospitalization from any cause,[317] reduce BP,[317, 408, 409] uric acid levels,[410] weight/fluid overload,[411] and reduce the risk of serious hyperkalemia.[412]

Harms

SGLT2i are well-tolerated with high levels of adherence in the RCTs in CKD.[317, 408, 409] In the studied populations, any risk of ketoacidosis or lower limb amputation resulting from SGLT2i use was substantially lower than the potential absolute benefits and generally restricted to people with diabetes. Meta-analysis estimates of absolute benefits and harms for each 1000 people with CKD and T2D treated for 1 year with an SGLT2i were 11 fewer cardiovascular deaths or hospitalizations for heart failure, for ~1 episode of ketoacidosis and ~1 lower limb amputation, respectively (and also 11 fewer people developing kidney disease progression and 4 fewer people with AKI). The corresponding benefits in people with CKD without diabetes were 15 fewer people with kidney disease progression, 5 fewer with AKI, and 2 fewer cardiovascular deaths or hospitalizations for heart failure per 1000 patient-years of treatment with no excess risk of ketoacidosis or amputation observed.[406] The vast majority of urinary tract infections in people taking SGLT2i are not caused by SGLT2 inhibition and there is no increased risk of hypoglycemia. There is an increased risk of mycotic genital

infections (in men and women), but these are generally mild and treating these infections with low-cost topical agents should help treatment adherence.

Certainty of evidence

SGLT2i have been studied in a series of large trials with consistent effects observed between trials, using different agents in the class. The trials have robust double-blind designs which minimize risk of bias and they have provided precise estimates of effect with no risk of publication bias due to the Nuffield Department of Public Health (NDPH) Renal Studies Group and SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART) collaboration brought together all the trialists that have conducted the relevant large trials. The totality of the evidence provides high levels of certainty of efficacy, with larger effect sizes observed in many populations. Relative effects on kidney disease progression appeared to be larger among people with higher levels of albuminuria, who are at highest absolute risk of progression. The size of relative risk reductions appear to be irrespective of the level of GFR, with no evidence of a threshold level of eGFR below which benefits start to attenuate.

For the 1A recommendation, also see the 2022 update to the KDIGO Clinical Practice Guideline in Diabetes Management for details of the certainty of the evidence.[19] Our ERT specifically also undertook a systematic review limited to people with CKD and no diabetes and considered the certainty of the effect in this subgroup to be moderate. The ERT identified the collaborative meta-analysis,[406] which included data from 2 RCTs evaluating an SGLT2i among adults with CKD without diabetes.[317, 408] Both RCTs were considered to have a low risk of bias. The collaborative meta-analysis harmonized the definition of CKD progression among the trials. The certainty of the evidence for CKD progression was graded as high (no concerns regarding the risk of bias of the studies or the consistency, directness, and precision of the results). The certainty of the evidence for the kidney failure outcome in people with CKD without diabetes was downgraded to moderate due to imprecision (although clear benefits are demonstrated in the CKD trials: Figure 19). Neither RCT reported on the critical outcome of hospitalizations for any cause in the subgroup without diabetes.

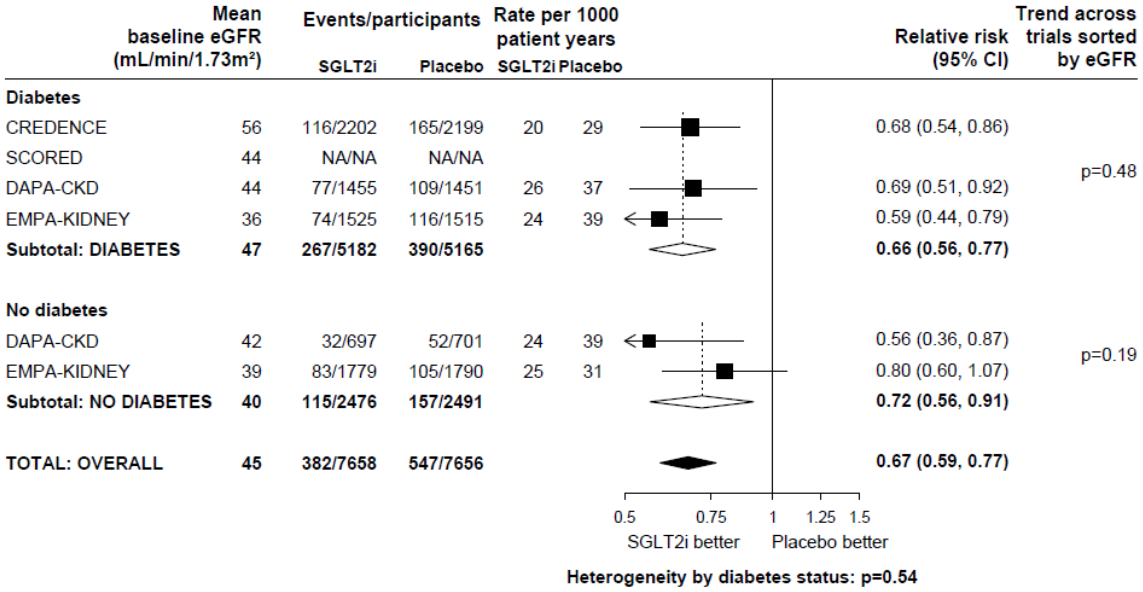


Figure 19. Effects of sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibition versus placebo on kidney failure (CKD trials). Kidney failure defined as a composite of sustained eGFR <15 ml/min per 1.73 m^2 (or eGFR <10 ml/min per 1.73 m^2 in EMPA-KIDNEY), maintenance dialysis, or kidney transplantation. Data for kidney failure not available for Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED).[413] CI, confidence interval; eGFR estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2.

Values and preferences

The Work Group judged that fully informed people with CKD with an indication for an SGLT2i would choose to receive SGLT2i for their proven benefits on risk of CKD progression, AKI, and a range of cardiovascular outcomes, their generally good safety profile, and simplicity to implement (assuming local availability and insurance coverage if required). SGLT2i also confer health benefits which may motivate people with CKD due to the reduced risk of hospitalization, and serious hyperkalemia and uric acid levels, all of which are common CKD complications.

Resource use and costs

Due to the high cost of KRT, SGLT2i have been found to be cost-saving in the people with CKD and diabetes recruited in the completed trials.[414] Generic SGLT2i are already available in some countries. From a healthcare system perspective, reducing the cost burden of hospitalizations and dialysis is highly desirable, and QoL may be preserved longer from their avoidance. Specifics as to whether people bear the costs of these medications will be country-dependent.

Considerations for implementation

The Work Group considered it safe to continue or even initiate an SGLT2i when the eGFR falls below 20 ml/min per 1.73 m^2 and continue their use until the time KRT is initiated (as was the approach used in the large CKD population RCTs[317, 408, 409]). We also

considered that initiating SGLT2i does not necessitate alteration of frequency of laboratory monitoring. It is not routinely necessary to recheck blood tests after initiating an SGLT2i in adults with CKD (see Practice Point 3.6.3).[317]

Reduced glomerular hyperfiltration resulting from SGLT2i can result in a dip in eGFR which is reversible. None of the large trials demonstrated an increased risk of AKI in people treated with SGLT2i (Figure 17), and the intervention does not induce hyperkalaemia (an important difference compared to inhibitors of the renin-angiotensin-aldosterone pathway which generally require additional monitoring after initiation [Figure 16]).

Rationale

Large trials individually and when combined in meta-analysis demonstrate clear net benefits of SGLT2i, with net benefits particularly large in people without diabetes due to almost no risk of serious harm from ketoacidosis or lower limb amputation.

Recommendation 3.6.3: We suggest treating adults with eGFR ≥20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g with an SGLT2i (2B).

This recommendation places high value on the potential for long-term use of SGLT2i in people without diabetes who have a substantially decreased GFR to reduce the risk of kidney failure but recognizes remaining uncertainty in this population due to the short follow-up in the RCTs. It also places moderate value on the benefits of SGLT2i on risk of AKI, cardiovascular death and myocardial infarction, and risk of hospitalization from any cause. SGLT2i also favorably reduce BP, uric acid levels, fluid overload, and the risk of serious hyperkalemia. Note that a person with CKD and heart failure has a clear indication for use of SGLT2i to reduce risk of cardiovascular death or hospitalization for heart failure irrespective of level of albuminuria (Figure 19).

Key information

Benefits and harms

Several large placebo-controlled RCTs have provided clear demonstrations of the efficacy of SGLT2i, which substantially reduce risk of kidney disease progression (Figure 17 & 19) as well as moderately reduce the risk of cardiovascular diseases (Figure 18) in people with and without CKD. Furthermore, a meta-analysis of the kidney disease progression outcome subdivided by primary kidney diagnosis demonstrated that there was no significant subgroup interaction by primary kidney diagnosis; that SGLT2i reduced the risk of AKI by 23% in people with or without diabetes (Figure 17).[406] SGLT2i also reduce the risk of hospitalization for any cause in people with CKD.[317] Some uncertainty remains about the effects on kidney disease progression in people without diabetes with urine ACR <200 mg/g, which led to a different grading of the recommendation for that population. EMPA-KIDNEY was the key trial to assess effects in people with CKD at risk of progression with urine ACR <200 mg/g and found evidence of significant interaction by ACR status for its primary outcome (trend p=0.02). Relative effects appeared to be larger in people with higher levels of

albuminuria. The slow rate of progression and small number of outcomes in the A1 subgroup limited the power for EMPA-KIDNEY to assess effects on the primary outcome in this subgroup. There were, however, important effects on chronic (i.e., long-term) slope in all albuminuria subgroups, and significant reductions in progression using total slope analyses over the 2 years of follow-up in the A2 and A3 groups considered separately (Figure 20).

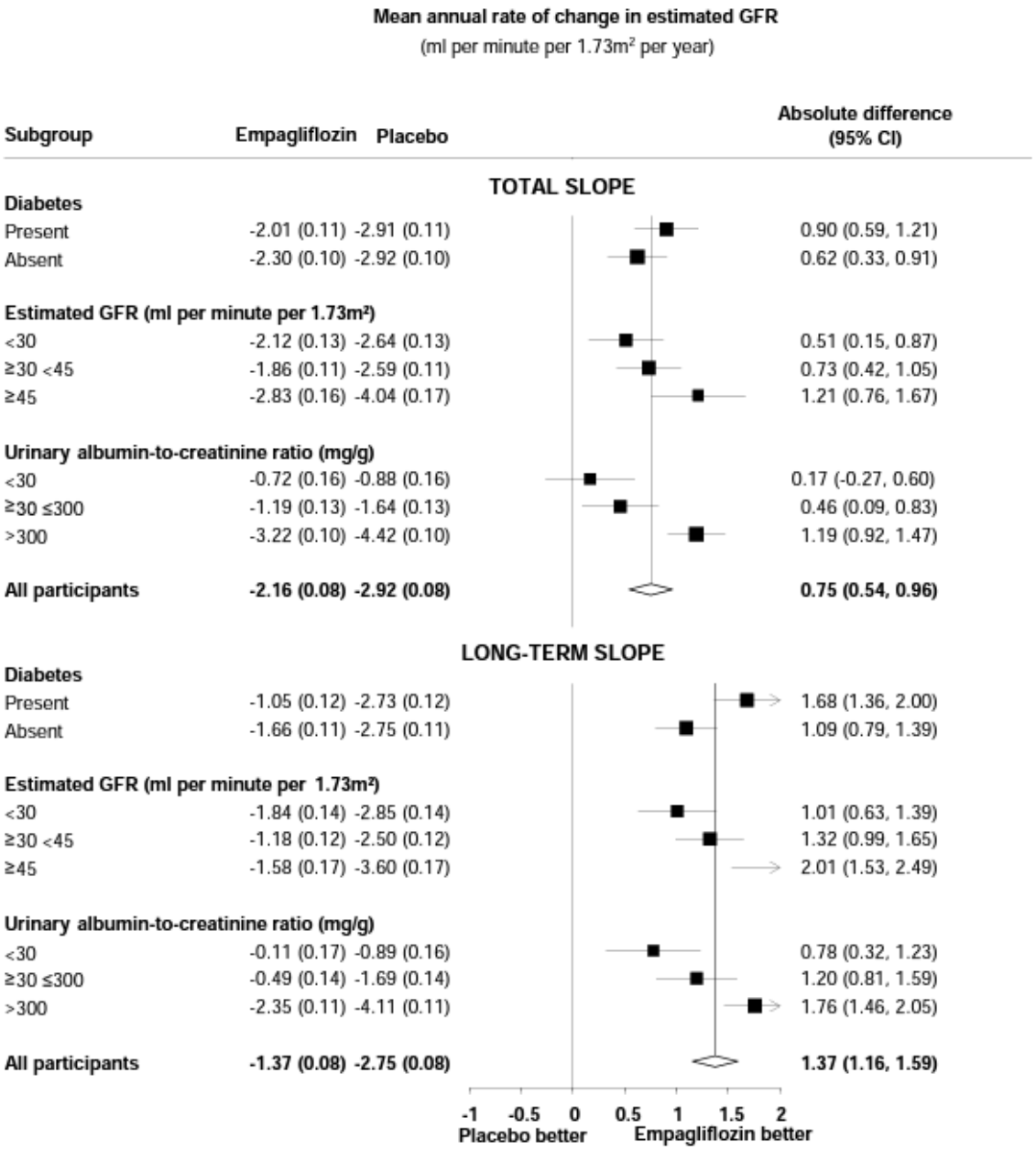


Figure 20. Effects of empagliflozin versus placebo on annual rate of change in estimated glomerular filtration rate (GFR) by key subgroups in The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY).[317]

Certainty of evidence

The overall certainty of evidence for the efficacy of SGLT2i to delay CKD progression in people with CKD without diabetes is moderate (see Supplementary Table S7). The ERT identified an individual participant data (IPD) meta-analysis,[406] which included data from 2 RCTs evaluating an SGLT2 inhibitor among adults with CKD but not diabetes.[317, 408] Both RCTs were considered to have a low risk of bias. The IPD meta-analysis harmonized the definition of CKD progression among the trials. The certainty of the evidence for CKD progression was graded as high as there were no concerns regarding the risk of bias of the studies or the consistency, directness, and precision of the results. The certainty of the evidence for kidney failure was downgraded to moderate due to imprecision. Neither RCT reported on the critical outcome of hospitalizations for any cause in the subgroup without diabetes.

Value and preferences

The Work Group judged that fully informed adults without diabetes and low levels of albuminuria (urine ACR <200 mg/g) who have established CKD and an eGFR of 20–45 ml/min per 1.73 m^2 may be particularly motivated to take SGLT2i for the benefits identified on rate of decline in GFR as they already have substantially reduced GFR. Adults with established CKD are highly likely to want to start treatment early in order to maximize benefits. Extrapolation of the findings from eGFR slope analyses (Figure 19) could mean substantial delays in any future requirement for KRT. People with CKD may also be motivated by the potential for SGLT2i to reduce risk of AKI, hospitalization, serious hyperkalemia, fluid overload, and uric acid levels, all of which are common CKD complications.

Resource use and costs

Health economic analyses are required in people with CKD without diabetes and low levels of albuminuria to establish their level of cost-effectiveness. From a healthcare system perspective, reducing the cost burden of hospitalizations and dialysis is highly desirable, and quality of life may be preserved longer from their avoidance. Specifics as to whether people bear the costs of these medications will be country-dependent.

Considerations for implementation

The considerations for implementation in people with CKD and low levels of albuminuria are no different to people with albuminuria (see above for details).

Rationale

Large trials considered individually and combined in meta-analysis demonstrate clear net benefits of SGLT2i, but evidence for benefits on CKD progression in people without diabetes and with low level levels of albuminuria is limited to eGFR slope analyses in heart failure trials and one CKD trial all with relatively short follow-up periods. However, extrapolation of these eGFR slope results suggests important benefits would accrue for such people if treated long-term.

Special considerations

Pediatric considerations

SGLT2i have not been tested in clinical trials on children with kidney disease. Limited observational data and phase II trial data exist for children with and without kidney disease. Four studies (99 children and young adults with diabetes and normal GFR) found pharmacokinetics and pharmacodynamics were likely to be the same in children and adults.[415-418] Recent work modelled pediatric dapagliflozin dosing for smaller children based on known pharmacokinetics and pharmacodynamics.[381] Side effects reported from the prior studies included an increase in glycosuria and infrequent reporting of nausea, genital infection, dehydration, and abdominal pain. In an RCT, there were no episodes of diabetic ketoacidosis and similar numbers of hypoglycemia between placebo and dapagliflozin, mostly occurring in those on insulin.[419]

There is limited research on kidney effects of SGLT2i in children. One study of 8 children with CKD and proteinuria found a reduction in 24-hour urine protein from a mean of 2.1 g/d to a mean of 1.5 g/d over 12 weeks.[420] Theoretically, the glycosuric effect of SGLT2i may lead to a negative calorie balance, interfering with optimal growth, especially in small children with underlying growth retardation. Clinical trials in the pediatric population are suggested, including in those with specific etiologies and at different age groups (i.e., prepubescent, peripubescent and postpubescent).

3.7. Mineralocorticoid receptor antagonists (MRAs)

The Work Group highlights a key recommendation and practice points from the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*.[19]

Recommendation 3.7.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an 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 3.7.1: 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 3.7.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.7.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 22).

Practice Point 3.7.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 3.7.5: 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.

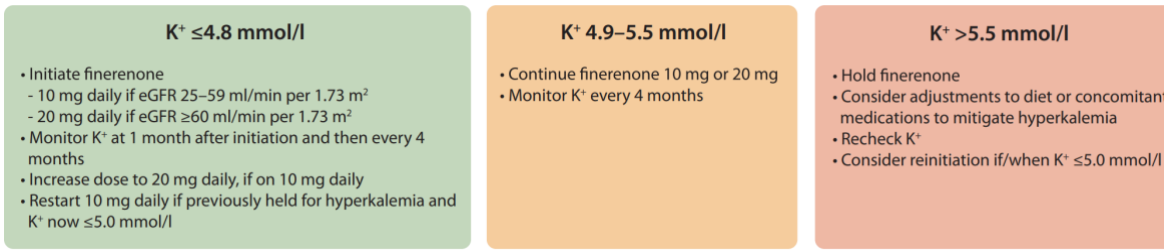


Figure 21. Serum potassium monitoring during treatment with a non-steroidal mineralocorticoid receptor antagonist (MRA) (finerenone). Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD). The United States Food and Drug Administration (FDA) has approved initiation of K^+ <5.0 mmol/l. This figure is guided by trial design and the FDA label and may be different in other countries. Serum creatinine/estimated glomerular filtration rate (eGFR) should be monitored concurrently with serum potassium.

MRAs reduce BP and albuminuria in people with CKD,[421] and are part of recommended care for heart failure with reduced ejection fraction.[422] The large Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-

DKD)[423] and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)[424] placebo-controlled trials, and their pooled analysis (FIDELITY),[425] demonstrated that the ns-MRA finerenone reduced cardiovascular risk in people with CKD and T2D (HR: 0.86; 95% CI: 0.78–0.95). The benefit was in large part due to a 22% reduction in the risk of hospitalization for heart failure (HR: 0.78; 95% CI: 0.66–0.92), with no clear effect on stroke (Figure 22).[425] These trials have some limitations on their generalizability to all people with CKD at risk of progression, given that study participants had an eGFR of 25 ml/min per 1.73 m^2, and ACR ≥30 mg/g, and that people without diabetes were excluded.

Whether based on laboratory data or investigator reports, finerenone approximately doubled the relative risk of hyperkalemia compared to controls. However, risks were generally low and average increase in serum potassium approximately 0.2–0.3 mEq from baseline values. The low absolute baseline risk of hyperkalemia may be due to the selection of participants with serum potassium <4.8 mmol/l and careful algorithmic monitoring of potassium during follow-up. Specific analyses of FIDELIO-DKD reported that 2.3% and 11.0% of participants in the finerenone group withdrew or interrupted treatment due to hyperkalemia (defined as serum potassium >5.5 mmol/l), respectively, versus 0.9% and 5.2% for the placebo group.[425] Overall, in FIDELITY, permanent treatment withdrawal for hyperkalemia was 1.7% versus 0.6%. Hospitalization for serious hyperkalemia was relatively rare with a <1% excess risk over 3 years.[426] Finerenone was also otherwise generally well-tolerated with no excess risk for serious AKI identified in the 2 large trials. Further details are available in the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*.[19]

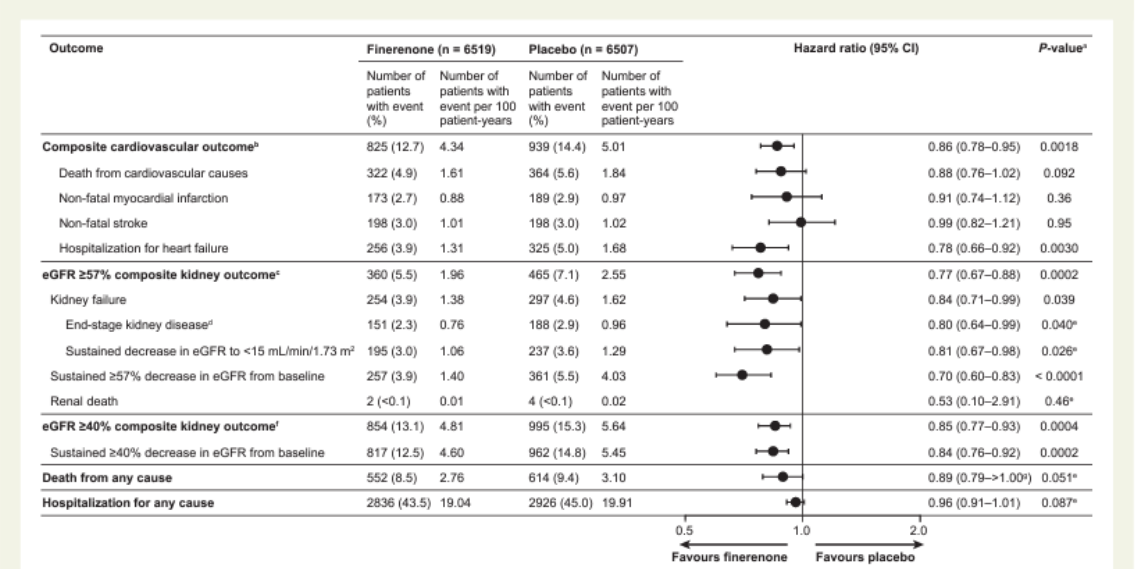


Figure 22. Effect of finerenone versus placebo on kidney and cardiovascular outcomes in pooled analyses from the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD trials). CI, confidence interval; eGFR, estimated glomerular filtration rate. Adapted from: Agarwal *et al.* Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. European Heart Journal Figure 2.[425]

Trials assessing the effect of combining an SGLT2i and finerenone compared to either alone are ongoing (ClinicalTrials.gov Identifier: NCT05254002). Adequately powered, large-scale, clinical outcome, placebo-controlled trials of steroidal and ns-MRAs have not been conducted in people with causes of CKD not related to diabetes, but are ongoing.[427]

Special considerations

Pediatric considerations

No relevant studies to inform this guideline have been completed in children.

3.8. Glucagon-like peptide receptor agonists (GLP-1 RA)

The Work Group highlights a key recommendation and practice point from the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*.[19]

Recommendation 3.8.1: 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 3.8.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Results of the FLOW trial assessing effects of GLP-1 RA in a dedicated CKD population are awaited. It is a definitive assessment of semaglutide on kidney outcomes in 3505 people with CKD, albuminuria, and T2D.[425] Nevertheless, extrapolating current evidence from trials in people with T2D where kidney function was generally preserved suggests GLP-1 RA safely improve glycemic control and may reduce weight and risk of CVD in people with CKD.[19,428] Meta-analysis of these large, placebo-controlled cardiovascular outcome GLP-1 RA trials has shown reduced MACE in people with prior CVD or at high risk.[428] The size of relative risk reductions on cardiovascular risk appear similar in people with or without decreased GFR.[428] Once aggregated, GLP-1 RA were shown to have modestly reduced risk of hospitalization for heart failure (HR: 0.89; 95% CI: 0.82–0.92), and separately reduced risk of death from any cause (HR: 0.88; 95% CI: 0.82–0.94).[428] The *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD* has recommended that long-acting GLP-1 RAs are prioritized ahead of insulin in people with T2D and CKD. GLP-1 RA with proven cardiovascular benefit which do not require dose adjustment in CKD include liraglutide, semaglutide (injectable), and dulaglutide.[19]

3.9. Metabolic acidosis

As GFR decreases, the kidney's ability to excrete hydrogen ions and generate bicarbonate decreases, resulting in the development of chronic metabolic acidosis. Metabolic acidosis is observationally associated with increased risk of protein catabolism, muscle wasting, inflammation, and other complications also associated with decreased eGFR such as impaired cardiac function and mortality.[429, 430] The causality of such associations remains to be demonstrated.

Definition and prevalence

Serum bicarbonate concentration begins to fall progressively once eGFR falls below 60 ml/min per 1.73 m^2 with reductions most evident in CKD stages G4–G5 (Figure 23, Table 24). Adjusted adult prevalence of serum bicarbonate <22 mmol/l was 7.7% and 6.7% in those with and without diabetes at stage G3, A1, respectively, increasing to 38.3% and 35.9% by CKD stage G5, A3.

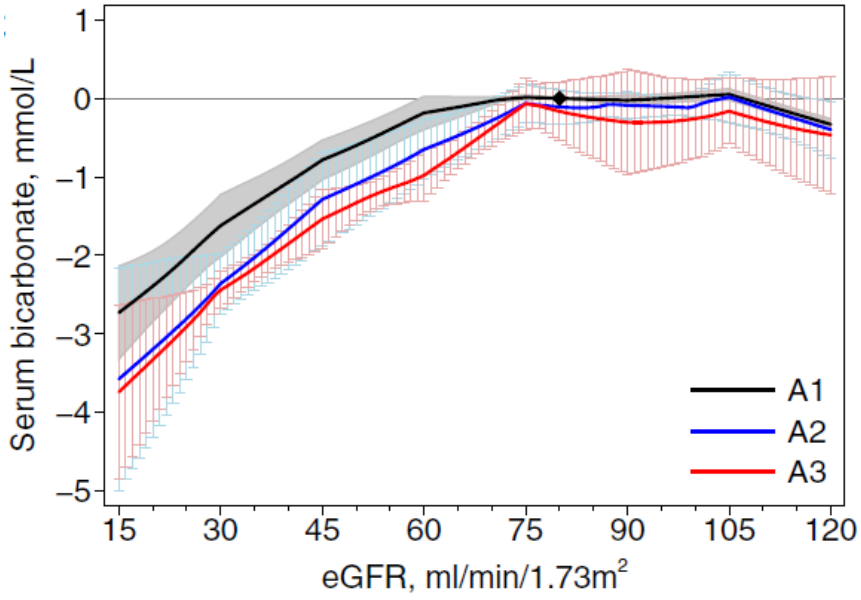


Figure 23. Association between estimated glomerular filtration rate (eGFR) with serum bicarbonate concentration in general population and high risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by level of albuminuria (A1–A3). The y axis represents the meta-analyzed absolute difference from the mean adjusted value at eGFR of 80 ml/min per 1.73 m^2 and albumin excretion <30 mg/g. Adapted from Inker *et al.* Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. AJKD Figure 2.[431]

Measure [Mean (SD)]	**Age**	**Sex**	**GFR category (ml/min per 1.73 m^2)**							
			105+	**90–104**	**75–89**	**60–74**	**45–59**	**30–44**	**15–29**	**0–14**
Bicarbonate	≥65	Female	27.4 (4.1)	27.1 (2.9)	26.9 (2.9)	26.8 (2.9)	26.5 (3.1)	25.9 (3.5)	24.8 (4.0)	24.0 (4.8)
		Male	27.1 (3.9)	26.6 (2.9)	26.7 (2.9)	26.5 (2.9)	26.1 (3.1)	25.3 (3.8)	24.1 (4.0)	24.2 (4.8)
	<65	Female	25.2 (2.8)	26.1 (2.8)	26.3 (2.8)	26.4 (2.9)	26.2 (3.2)	25.1 (3.6)	23.6 (4.2)	24.0 (5.0)
		Male	26.4 (2.8)	26.5 (3.0)	26.6 (2.7)	26.5 (2.9)	25.9 (3.2)	24.8 (4.4)	23.5 (4.1)	24.4 (4.7)

Table 24. Variation of laboratory values in a large population database* by age group, sex and estimated glomerular filtration rate (eGFR); bicarbonate, mmol/l, mean (standard deviation), n = 3,990,898. *Data from the Optum Labs Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data. The database contains longitudinal health information on enrollees and patients, representing the diversity of geographical regions across the United States.

Practice Point 3.9.1: In people with CKD, consider using dietary and/or pharmacological treatment to prevent severe acidosis (e.g., bicarbonate <16 mmol/l).

Practice Point 3.9.2: Monitor people with CKD to ensure correction of serum bicarbonate does not result in concentrations exceeding the upper limit of normal and does not adversely affect BP control, serum potassium, or fluid status.

The Work Group have not provided a graded recommendation for the treatment of acidosis due to a lack of large-scale RCTs supporting its use. In 2012, a 2B recommendation was justified because alkali supplementation may be a promising low-cost, high-benefit adjunct treatment for people with CKD and may be accessible to all populations. This was based on an RCT that had suggested potential kidney progression and nutritional benefits with no important increase in BP or heart failure complications.[1] However, since 2012, a number of trials testing the hypothesis that sodium bicarbonate therapy slows kidney disease progression have reported, including several employing placebo control. A 2020 systematic review identified 15 trials with ≥3 months of follow-up in people with CKD (eGFR <60 ml/min per 1.73 m^2 and/or proteinuria) comparing the effects of oral sodium bicarbonate versus placebo or versus no study medication on kidney outcomes. Of the 15 trials (2445 participants, median follow-up 12 months), 11 were published since 2012. The totality of the evidence remains limited by a low number of outcomes and meta-analysis restricted to the placebo-controlled trials does not confirm any important modifying effect of oral sodium bicarbonate versus placebo on risk of kidney failure (HR: 0.81; 95% CI: 0.54–1.22).[432] The largest placebo-controlled trial of oral sodium bicarbonate was conducted by the Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older people with chronic kidney disease and low-grade acidosis (BiCARB) Study Group.[433] It contributed 33/152 versus 33/148 kidney failure outcomes to the meta-analysis in its bicarbonate versus placebo arms, respectively (HR: 0.97; 95% CI: 0.64–1.49). Importantly, the BiCARB trial, which studied people with CKD G3–G4 aged ≥60 years and sodium bicarbonate concentration <22 mmol/l, also found no evidence of benefit on non-kidney outcomes to support oral sodium bicarbonate supplementation (the primary outcome was based on the Short Physical Performance Battery at 12 months, and secondary outcomes included generic and disease-specific QoL assessments, anthropometry, kidney function, walk distance, BP, and bone and vascular health markers). Allocation to oral sodium bicarbonate was associated with higher costs and lower European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) assessed QoL over 1 year.[433]

Licensed non-alkali oral interventions may be an alternative to oral sodium bicarbonate to treat metabolic acidosis, but have not been shown to have particular advantages.[434, 435] Although placebo-controlled trials have found no good evidence that correcting sodium bicarbonate levels have important effects on clinical outcomes, the Work Group concluded that the intervention is clearly effective at increasing serum bicarbonate concentration, and is a suitable treatment to avoid more severe acidosis (e.g., <16 mmol/l).

Dietary approaches

Dietary modifications that limit the consumption of acid-rich foods and/or increase the intake of alkaline-rich foods reduce the net endogenous acid production and can serve as an additional strategy to control metabolic acidosis in people with CKD.[436, 437] Such diets are generally low in animal protein or have a higher consumption of plant-based foods over animal-based foods (i.e. plant-dominant diets such as Mediterranean or vegetarian diets). Four small RCTs of alkaline-rich plant-based diets in adults with CKD demonstrate a comparable benefit to oral sodium bicarbonate in controlling metabolic acidosis.[438-441]

Special considerations

Pediatric considerations

As in adults, children with CKD often have metabolic acidosis. In the CKiD and The Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study (4C) studies, 38%–60% of children had a serum bicarbonate of <22 mmol/l, varying by CKD category. Low bicarbonate was associated with increased risk of disease progression.[309, 442] It should also be noted that for younger children the normal range for sodium bicarbonate is as low as 17 mmol/l. In children, metabolic acidosis is also likely to cause growth retardation. Data from the observational CKiD study revealed that prepubertal children with acidosis who were treated with alkali had improved growth.[443] In children with normal GFR but renal tubular acidosis, prolonged acidosis can also result in poor growth. The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on bone metabolism for children with CKD recommend prevention of acidosis in children to optimize growth.[444] There have not been any trials of the effect of bicarbonate supplementation on CKD progression or growth in children.

3.10. Hyperkalemia in CKD

Definition and prevalence

Potassium is key to cell membrane electrophysiology, with abnormalities predisposing to abnormal cardiac conduction and arrhythmias. The kidneys play a key role in potassium homeostasis with decreased GFR generally associated with increased potassium concentration (Table 25; Figure 24). The definition of hyperkalemia is based on the distribution of potassium values in the general population. Hyperkalemia is uncommon when the eGFR is >60 ml/min per 1.73 m^2 and increases in prevalence with lower GFR.

Measure [Mean (SD)]	Age	Sex	GFR category (ml/min per 1.73 m^2)							
			105+	**90–104**	**75–89**	**60–74**	**45–59**	**30–44**	**15–29**	**0–14**
Potassium	≥65	Female	4.1 (0.5)	4.2 (1.3)	4.2 (0.5)	4.3 (0.5)	4.3 (1.3)	4.4 (0.5)	4.5 (1.0)	4.5 (2.0)
		Male	4.2 (0.5)	4.3 (0.6)	4.3 (1.1)	4.4 (0.6)	4.4 (0.7)	4.5 (1.1)	4.6 (0.6)	4.6 (1.6)
	<65	Female	4.1 (0.7)	4.2 (1.3)	4.3 (17.0)	4.2 (1.0)	4.3 (0.5)	4.3 (0.6)	4.4 (0.6)	4.5 (1.1)
		Male	4.2 (0.4)	4.3 (0.5)	4.3 (0.6)	4.3 (0.4)	4.4 (0.5)	4.5 (0.6)	4.5 (0.7)	4.6 (0.7)

Table 25. Variation of laboratory values in a large population database* by age group, sex and estimated glomerular filtration rate (eGFR); potassium, mmol/l, mean (standard deviation), n = 4,278,600. *Data from the Optum Labs Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data. The database contains longitudinal health information on enrollees and patients, representing the diversity of geographical regions across the United States.

Adults with CKD G3, A1 in the general and high-risk population cohorts, contributing to the CKD Prognosis Consortium, had an adjusted prevalence of hyperkalemia (defined as a serum potassium >5.0 mmol/l) of 8.8% and 4.5% in those with and without diabetes, respectively; increasing to 34.4% and 23.7% by CKD G5, A3 (Figure 25).[431] Note that there is variability in prevalence of hyperkalemia, and it is not inevitable at lower levels of GFR, thus understanding potassium physiology and impacting factors are important in effective patient care.

Hyperkalemia in people with preserved GFR is less prevalent. An acute episode of hyperkalemia is a potassium result above the upper limit of normal that is not known to be chronic. At the current time, there is no consensus on the magnitude, duration and frequency of elevated potassium values that define chronicity.[445] In addition to decreased eGFR, other risk factors for hyperkalemia included higher ACR and prior diabetes, hyperglycemia, constipation, RAS inhibitors[446] and MRA.[426] Note that SGLT2i do not appear to increase serum potassium values.[317, 412]

Studies have demonstrated a continuous U-shaped relationship between serum potassium and all-cause mortality in a range of different populations (Figure 26).[447, 448] It has also been associated with worse kidney prognosis.[449] Observationally, the risk of death from the same degree of hyperkalemia is lower in more advanced CKD stages.[450-454] This may suggest that there are adaptive mechanisms that render better tolerance to elevated levels of potassium in circulation.[450, 455-458]

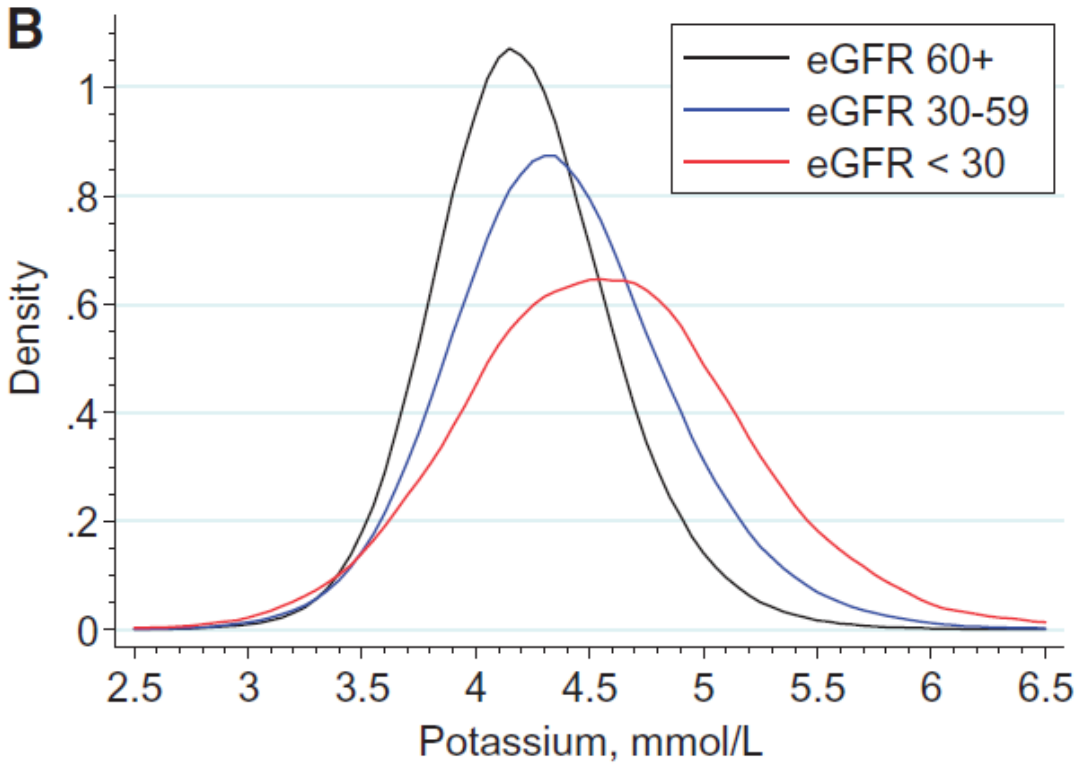


Figure 24. Distribution of blood potassium in general population and high-risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by estimated GFR (eGFR). Reproduced from Kovesdy *et al*. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. European Heart Journal Figure 1.[447]

Unpublished data still under review

Figure 25. Meta-analyzed adjusted hyperkalemia (25th & 75th percentile cohort) in general population and high-risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by diabetes status. Hyperkalemia is defined as potassium >5 mmol/l. The adjusted prevalence of hyperkalemia at each estimated glomerular filtration rate (eGFR) and albuminuria stage was computed as follows: first, the random-effects weighted adjusted mean odds at the reference point (eGFR 50 ml/min per 1.73 m^2) was converted into a prevalence estimate. To the reference estimate, the meta-analyzed odds ratios for hyperkalemia was applied to obtain prevalence estimates at eGFR 95, 80, 65, 35, and 20 ml/min per 1.73 m^2 for each stage of albuminuria. The prevalence estimates were adjusted to 60 years old, half male, non-black, 20% history of CVD, 40% ever smoker, and body-mass index 30 kg/m^2. The 25th and 75th percentiles for predicted prevalence were the estimates from individual cohorts in the corresponding percentiles of the random-effects weighted distribution of adjusted odds. A1, albuminuria <30 mg/g [<3 mg/mmol]; A2, albuminuria 30–300 mg/g [3–30 mg/mmol]; A3, >300 mg/g [>30 mg/mmol]. Adapted from Inker et al. Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. AJKD Figure S20.[431]

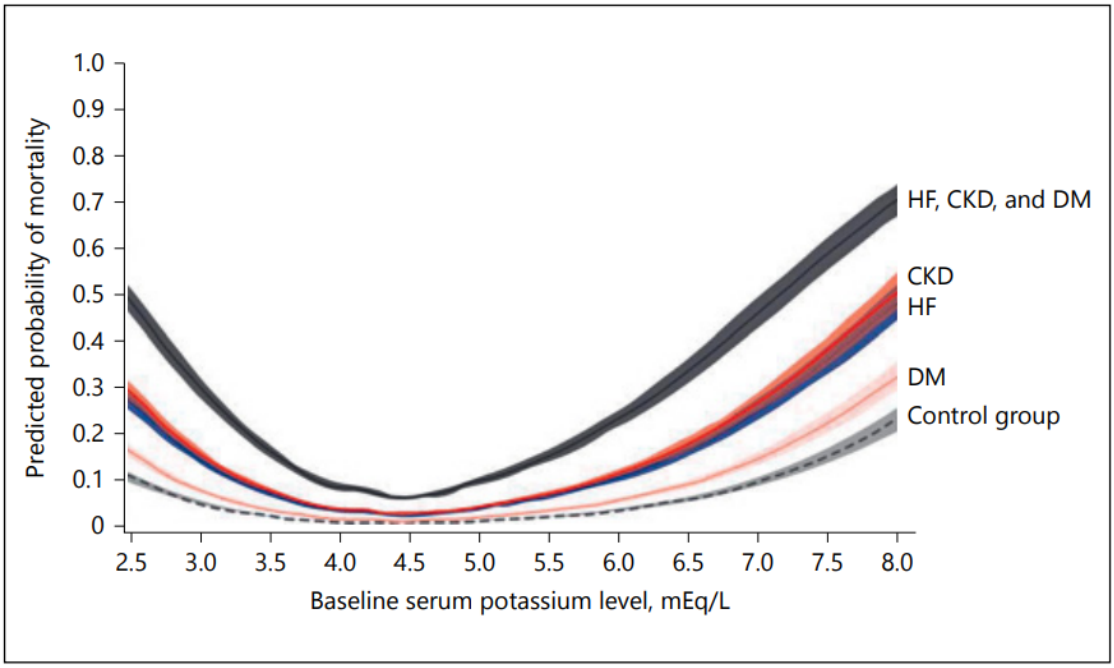


Figure 26. Serum potassium concentration and confounder-adjusted risk of death by presence or absence of diabetes, heart failure or CKD. Reproduced from Collins et al.2017 Nephrol Figure 2.[448]

3.10.1. Awareness of factors impacting on potassium measurement

There are several factors and mechanisms that may impact on potassium measurements, including the actions of medications that can increase the risk of developing hyperkalemia. These are summarized in Tables 26 and 27.

Practice Point 3.10.1.1: Be aware of the variability of potassium laboratory measurements as well as factors and mechanisms that may influence potassium measurement including diurnal variation, plasma versus serum samples, and the actions of medications.

Factor/mechanism	Possible cause/clinical implication
Pseudohyperkalemia -*In vivo* serum potassium is normal and commonly GFR preserved, but during the process of drawing blood or clotting, here has been a release of intracellular potassium	• Tight tourniquet • Hand/arm exercising or clenching at the time of blood draw • Hemolysis due to vigorous shaking of blood vial/inappropriate blood draw equipment/inappropriate storage of samples • If suspected, blood should be retaken and analyzed in the appropriate manner and time frame[445, 459] • Presence of thrombocytosis/leukocytosis • If suspected, take plasma potassium as serum potassium may be falsely increased[460]
Hyperkalemia due to disruption in the mechanism of shifting potassium out of cells	• Increase in plasma osmolarity (e.g., dehydration, hyperglycemia) • Massive tissue breakdown (e.g., rhabdomyolysis, tumor lysis syndrome) • Beta adrenergic blockade, especially during and immediately after exercise[459] • Insulin deficiency • Aldosterone blockade • Non-organic acidosis
Hyperkalemia due to disruption in the mechanism of moving potassium into cells	• Disruption in the release of insulin in response to raised serum potassium (e.g., in uncontrolled diabetes) • Disruption to the release of aldosterone in response to a raised serum potassium[459]
Hyperkalemia due to decreased ability to excrete potassium	• Advancing CKD resulting in inability to excrete excessive potassium • Constipation: In advancing CKD, the gut assumes a much more important role in maintaining potassium balance by increasing the excretion of potassium[461, 462] • Medications: Blocking the RAAS pathway and other medication resulting in the inability to excrete excessive potassium (Table 27)[459, 463]
Diurnal variation in potassium excretion with most excretion in humans occurring close to noon	Circadian excretion of kidney electrolytes have been well documented.[464] Clinical relevance is yet to be understood Note the 0.24–0.73 mmol/l variation in K+ values within individuals over a 24-hour period
Plasma vs. serum potassium values	Potassium values differ between serum and plasma values with serum values being typically higher. Healthcare providers need to be aware of the right reference values for the sample[460]
Postprandial hyperkalemia	As kidney function declined in CKD, there is a corresponding decline in the ability of the kidneys to increase kaliuresis postprandially, eventually becoming insufficient to maintain external potassium balance[465]

Table 26. Factors and mechanisms that impact on potassium measurements. [445, 459-465]

Class	Mechanism	Example
ACEi	Inhibit conversion of angiotensin I to angiotensin II	Captopril, lisinopril, perindopril, etc.
ARB	Inhibit activation of angiotensin I receptor by angiotensin II	Losartan, irbesartan, candesartan, etc.
Aldosterone antagonist	Block aldosterone receptor activation	Spirolactone, eplerenone, finerenone
B-adrenergic receptor blocker	Inhibit renin release	Propranolol, metoprolol, atenolol
Digitalis glycoside	Inhibit Na^+-K^+-ATPase; necessary for collecting K^+ secretion	Digoxin
Heparin	Reduced production of aldosterone	Heparin sodium
Potassium-sparing diuretic	Block collecting duct apical Na^+ channel, decreasing gradient for K^+ secretion	Amiloride, triamterene
NSAIDs	Inhibit synthesis of prostaglandin E and prostacyclin, inhibiting renin release	Ibuprofen, naproxen. diclofenac, etc.
Other	Block collecting duct apical Na+ channel, decreasing gradient for K^+ secretion	Trimethoprim, pentamidine
CNI	Inhibit Na^+-K^+-ATPase; necessary for collecting K^+ secretion	Cyclosporine and tacrolimus
ns-MRA	Blocks MR-mediated Na^+ reabsorption	Finerenone

Table 27. Medications associated with increased risk of hyperkalemia. ACEi, angiotensin-converting enzyme inhibitor; ; ARB, angiotensin II receptor blocker; ATP, adenosine triphosphate; CNI, calcineurin inhibitor; K^+, potassium; NA^+, sodium; NSAID, nonsteroidal anti-inflammatory drugs; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist;. Weiner ID, et al. Comprehensive Clinical Nephrology 2015;111-123;[466] KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD.[19]

The Work Group would like to highlight a Figure 21 for the monitoring of serum potassium during treatment with a non-steroidal MRA (finerenone) from the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD*.[19]

Hyperkalemia has been associated with therapeutic actions of either reducing or stopping RASi.[467-470] Steps can be taken to mitigate risk of hyperkalemia and improve potassium control that could increase the use of RASi in people with an evidenced indication. For details on how to manage hyperkalemia associated with the use of RASi and associated monitoring, please refer to Figure 16. See Section 4.3 for more information on continuing RASi after hyperkalemia events.

3.10.2. Potassium exchange resins

Practice Point 3.10.2.1: Be aware of local availability or formulary restrictions with regards to the pharmacologic management of nonemergent hyperkalemia.

The pharmacologic management of nonemergent hyperkalemia has new clinical tools with the availability of new potassium-exchange resins. These resins have differing mechanisms of action, onsets of clinical effects, and potential medication and disease-state interactions (Table 28). Whilst the classic potassium exchange resins have had tolerability issues, the newer potassium exchange resins appear to have less such issues and appear relatively safe when used long term use.[465, 471, 472] Use of these newer medications may help facilitate essential use of RASi/MRA. However, it is important that the healthcare provider be aware of clinical nuances and local availability or formulary restrictions in determining therapy selection.[473] A comparison of available potassium exchange resins can be found in Table 28.

	(Polystyrene sulfonates) sodium or calcium	Patiromer	Sodium zirconium cyclosilicate (SZC)
Mechanism of action	Sodium-potassium exchange resin (SPS) or calcium-potassium exchange resin (CPS)	Calcium-potassium exchange polymer	Crystalline compound that traps K^+ in exchange for hydrogen and sodium cations
Counterion content	100 mg sodium per gram of SPS 1.6–2.4 mmol of calcium per gram of CPS	1600 mg calcium per 8.4 gram patiromer	400 mg sodium per 5 g of SZC
Cations bound	Potassium, magnesium, calcium	Potassium, magnesium	Potassium
Formulation of route of administration	Powder for reconstitution (oral), suspension (oral), and enema (rectal)	Powder for reconstitution (oral)	Powder for reconstitution (oral suspension)
Dosage and titration	Oral: 15–60 g/d (up to 4 times per day) Rectal: 30 g/d (for SPS up to a maximum of 50 g/d)	Initial: 8.4 g orally once per day (maximum 25.2 g orally once per day); dose ca be increased by 8.4 g increments at 1-week intervals	Initial: 10 g orally 3 times per day for 48 hours
Maintenance dosing	15–60 g/d orally per day depending on potassium level and level of tolerability	8.4–25.2 g orally once per day	5–10 g once per day
Onset of effect	Variable, hours to days	4–7 hours	1–6 hours
Duration of effect	Variable, 6–24 hours	12–24 hours	Unclear
Administration pearls	Separate from oral medications by at least 3 hours before or 3 hours after administration; if gastroparesis, separate other medications by 6 hours	Separate from oral medications by at least 3 hours before or 3 hours after administration	Separate from other oral medications by at least 3 hours with clinically meaningful gastric pH-dependent bioavailability by at least 2 hours before or after administration
Adverse effects	GI events (nausea, vomiting, diarrhea, constipation), electrolyte disturbances (hypokalemia,	GI events (nausea, diarrhea, flatulence), electrolyte disturbances	GI events (nausea, diarrhea, constipation), electrolyte disturbances

	hypocalcemia, hypomagnesemia), edema, and potentially serious GI adverse events (intestinal necrosis, bleeding, ischemic colitis, perforation)	(hypokalemia, hypocalcemia, hypomagnesemia). Not enough post-marketing surveillance at present to evaluate long-term/rare events.	(hypokalemia, hypocalcemia, hypomagnesemia), and edema. Not enough post-marketing surveillance at present to evaluate long-term/rare events

Table 28. A comparison of potassium exchange resins. *GI, gastrointestinal.* Modified from Bridgeman et al, *Nephrology Dialysis Transplantation*, Volume 34, Issue Supplement 3, December 2019, Table 1.[473]

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

"Think Kidneys" and the UK Kidney Association have provided a practical guide which we have adapted (Table 29) for repeat testing after a hyperkalemic episode.[474] The timing of repeat testing is guided by the level of hyperkalemia and the clinical context.[475]

Severity of hyperkalemia	Clinically unwell or AKI	Unexpected result
Moderate K^+ 6.0–6.4 mmol/l	Assess and treat in hospital	Repeat within 24 hours
Severe K^+ ≥6.5 mmol/l	Take immediate action to assess and treat	

Table 29. Suggested action in the event of moderate and severe hyperkalemia. K^+, potassium
Modified from 'Think Kidneys' 2017 and the UKKA Clinical Guideline on Hyperkalemia 2020

3.10.4. Managing hyperkalemia

In people with CKD and the management of non-emergent hyperkalemia, a systematic approach of treating correctable factors (e.g., correction of severe metabolic acidosis) and understanding the role of diet and medications may provide a pragmatic framework. Figure 27 shows a stepwise practical approach to the management of hyperkalemia in CKD.

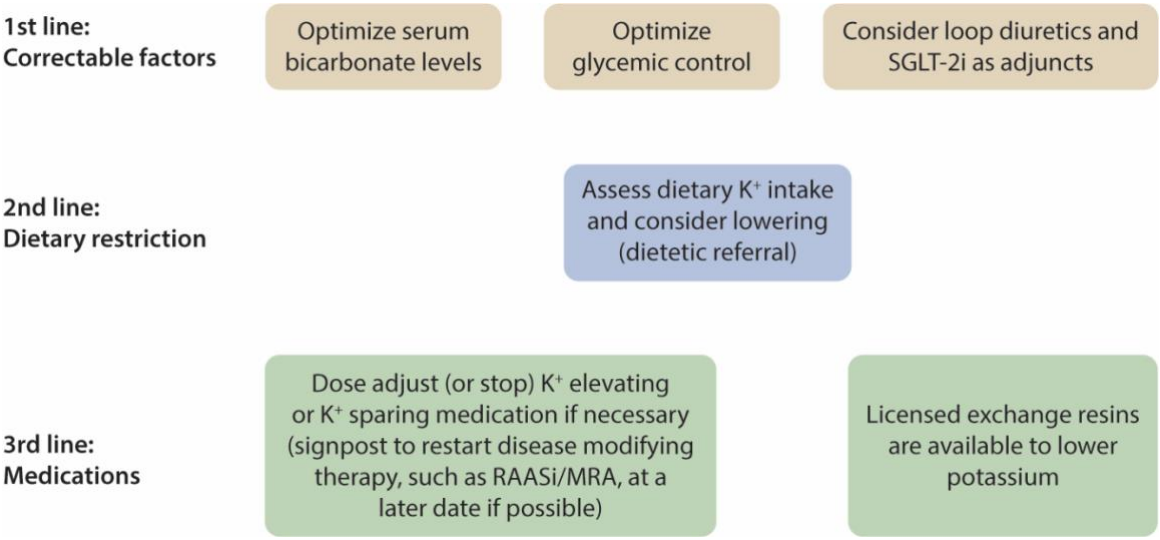


Figure 27. Actions to manage hyperkalemia (potassium >5.5 mmol/l) in chronic kidney disease (CKD). K^+, potassium; MRA, mineralocorticoid antagonists; RASi, renin-angiotensin system inhibitors; SGT2i, sodium-glucose cotransporter-2 inhibitors

3.10.5. Dietary considerations

In early stages of CKD, higher potassium intake appears to be protective against disease progression[476] and dietary restriction of potassium may be harmful to cardiac health; therefore, is not endorsed.

Practice Point 3.10.5.1: For those people with CKD G3–G5 and emergent hyperkalemia, an individualized approach that includes dietary and pharmacologic interventions and takes into consideration associated comorbidities and quality of life is advised. Assessment and education through a registered dietitian or accredited nutrition providers is advised.

Practice Point 3.10.5.2: 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.

Diet increases serum potassium postprandially,[465, 477, 478] but other conditions such as the use of potassium-sparing medications, metabolic acidosis, hyperosmosis due to hyperglycemia, hypernatremia or uremia, and constipation are more likely explain potassium abnormalities than diet.[436, 445, 462, 479] While short-term dietary restriction of the foods highest in potassium is a valid strategy to treat acute hyperkalemia, restriction of foods highest in bioavailable potassium may be a supportive prevention strategy for people with a history of hyperkalemia or during periods in which hyperkalemia risk is a concern.[480] Increased efforts toward education on potassium content in foods can serve to improve diet quality and diversity for many people with CKD where this restriction may not be needed.[436, 445, 481] Although guidelines and available information to people with CKD have heavily emphasized plant-based foods as potential causes of hyperkalemia in CKD,[482] other healthy nutrients in plant-based foods affect potassium absorption and distribution,[477, 483, 484] therefore, the net bioavailable potassium from plant-based foods is lower than appreciated.[485] Highly processed foods (rich in potassium additives), meats and dairy products, juices, and salt substitutes made with potassium chloride are actually higher in absorbable potassium than many plant-based, fresh foods (Figure 28).[486-488]

Teaching materials used with people with CKD should place a greater focus on highly processed versus unprocessed food restriction, for hyperkalemia management.[482] An example of a patient resource for potassium management can be found at: http://www.bcrenal.ca/resourcegallery/Documents/Potassium_Management_in_Kidney_Disease.pdf

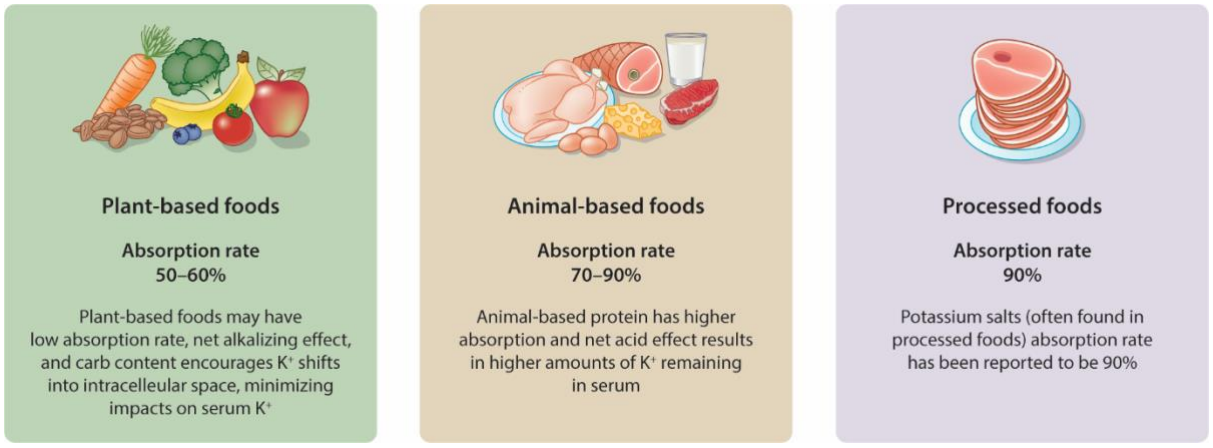


Figure 28. Potassium absorption rates of plant-based, animal-based, and processed foods. *Journal of Renal Nutrition*, Vol 31, No 2 (March), 2021: 210-214

Cooking methods such as soaking foods for 5–10 minutes in previously boiled water can effectively reduce the potassium by half for some foods.[489] Thus, educating people with CKD and healthcare providers, using clear messaging, on dietary approaches to potassium management is needed (https://www.theisn.org/initiatives/raasi-toolkit/), as well as a policy to improve food labelling by detailing the added potassium used in processing.

Special considerations

International considerations

For people with CKD and severe recurrent hyperkalemia (potassium >6 mmol/l) the balance to be considered is between the additional cost of the number needed to treat with potassium binders to prevent additional costs of hyperkalemia over and above CKD management costs. If the price for potassium-binding therapy is lower than the reduction of inpatient and outpatient costs due to prevented hyperkalemia, the cost-benefit ratio will be favorable because in addition to the health benefits, there is a net saving of healthcare costs resulting from potassium-binding treatment. Key is to implement a successful affordable strategy for hyperkalemia management that allows maintenance of other therapies directed at reducing both progression of CKD and reduction in MACE.

3.11. Anemia

The *KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease* will be updated in 2024.[59]

Mean hemoglobin is, on average, lower in both men and women with an eGFR <60 ml/min per 1.73 m^2 compared to health adults and progressively falls with decreasing GFR (Table 30; Figure 29). For example, adults with CKD G3, A1 in the general and high-risk population cohorts contributing to the CKD Prognosis Consortium had an adjusted prevalence of anemia (hemoglobin <12 g/dl in men; <11 g/dl in women) of 14.9% and 11.5% in those with and without diabetes, respectively. Increasing to 60.7% and 57.4% by CKD G5, A3. Note that a drop in Hb is expected in pregnancy (physiologic anemia) and may not warrant treatment (although the cutoff at which treatment is desirable is unclear and requires

clinical judgement. Refer to the *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease* publications for specific recommendations, selection, and dosing of specific therapeutic agents, and research recommendations.

Measure [Mean (SD)]	Age	Sex	GFR category (ml/min per 1.73 m^2)							
			105+	90–104	75–89	60–74	45–59	30–44	15–29	0–14
Hemoglobin	≥65	Female	12.2 (2.0)	13.2 (4.6)	13.2 (1.7)	13.2 (1.5)	12.8 (1.6)	12.1 (1.7)	11.2 (1.8)	10.3 (1.7)
		Male	12.9 (2.4)	14.2 (1.8)	14.2 (1.7)	14.1 (1.8)	13.5 (1.9)	12.7 (2.0)	11.5 (2.0)	10.5 (2.0)
	<65	Female	13.0 (1.4)	13.3 (1.3)	13.4 (2.0)	13.4 (1.4)	13.0 (1.6)	12.1 (1.8)	11.0 (1.9)	10.6 (2.5)
		Male	14.9 (1.5)	15.0 (3.1)	15.0 (1.4)	14.9 (1.6)	14.1 (2.0)	12.9 (2.2)	11.7 (2.2)	10.9 (2.0)

Table 30. Variation of laboratory values in a large population database* by age group, sex and estimated glomerular filtration rate (eGFR); hemoglobin, g/d/l, mean (standard deviation), n = 3,561,622. *Data from the Optum Labs Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data. The database contains longitudinal health information on enrollees and patients, representing the diversity of geographical regions across the United States.

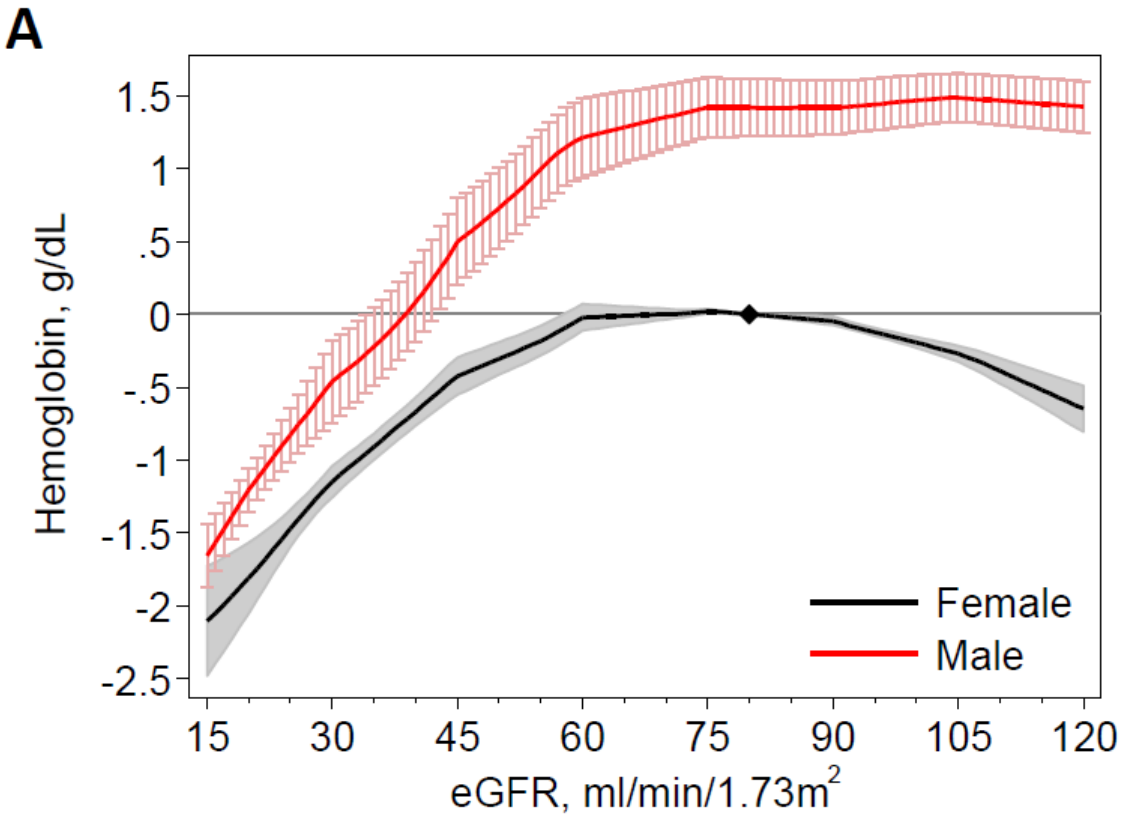


Figure 29. Association between estimated glomerular filtration rate (eGFR) and hemoglobin concentration from general population and high risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by diabetes status. Adapted from Inker *et al.* Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. AJKD Figure S20.[431]

3.12. CKD-Mineral Bone Disorder (CKD-MBD)

The Work Group highlights the *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)*.[16] Please refer to this publication for specific recommendations, selection, dosing of specific therapeutic agents, and research recommendations.

Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as eGFR declines (Figure 30). These are detectable as abnormalities of serum calcium, phosphate, vitamin D metabolites and circulating hormones (i.e., parathyroid hormone [PTH] and fibroblast growth factor-23). These changes are grouped under the umbrella term CKD-MBD which also includes renal osteodystrophy and extraskeletal (i.e., vascular) calcification related to these abnormalities of metabolism. It has been recommended that in people with CKD G3a–G5, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels considered together.[16]

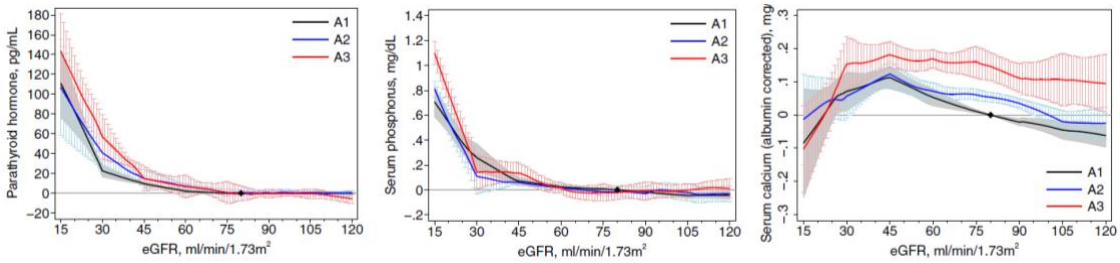


Figure 30. Association between estimated glomerular filtration rate (eGFR) with concentrations of parathyroid hormone, serum phosphate and serum calcium in general population and high risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by level of albuminuria (A1–A3). The y axis represents the meta-analyzed absolute difference from the mean adjusted value at eGFR of 80 ml/min per 1.73 m^2 and albumin excretion <30 mg/g. A1, albuminuria <30 mg/g [<3 mg/mmol]; A3, >300 mg/g [>30 mg/mmol]. Adapted from Inker *et al.* Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. AJKD Figure 2.[431]

Higher serum phosphate concentrations are associated with mortality,[490] and experimental data suggest that serum phosphate concentration is directly related to bone disease, vascular calcification,[491, 492] and CVD. Low-phosphorus diets and binders are used to help lower serum phosphate to reduce the long-term complications of CKD-MBD, although more research is needed to fully understand the disease-modifying impact of these interventions.[493] Similarly, despite evidence suggesting no benefit on clinical outcomes,[494] vitamin D replacement and calcimimetics to control PTH levels and to maintain calcium within the normal range are also common strategies. For recommendations regarding selection and dosing with specific therapeutic agents and research, please see published specific *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation,*

Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD).[16]

3.13. Hyperuricemia

Definition and prevalence

Uric acid is the end product of the metabolism of purine compounds, and both increased urate production and decreased kidney excretion of uric acid can lead to hyperuricemia. The American College of Rheumatology define hyperuricemia as a serum uric acid concentration of ≥6.8 mg/dl (≥~400 µmol/l).[495]

Data from the US National Health and Nutrition Examination Survey (NHANES) 2015–2016 found that the crude adult prevalence of gout (defined as self-reported, doctor diagnosis, or uric acid-lowering therapy use) was 3.9% with a higher prevalence in men than women (5.2% vs. 2.7%). After adjustment for age and sex, an eGFR consistent with CKD G3 was associated with about twice the prevalence of gout (odds ratio [OR]: 1.96; 95% CI: 1.05–3.66).[496]

Recommendation 3.13.1: We recommend people with CKD and symptomatic hyperuricemia should be offered uric acid-lowering intervention (1C).

The Work Group placed high value on avoiding the unpleasant symptoms of acute gout and preventing long-term complications of recurrent gout among people with CKD. There are well-tolerated and low cost oral medications that can effectively lower blood uric acid concentration in people with CKD.

Key information

Balance of benefits and harms

Systematic review of the management of gout by the American College of Rheumatology found strong evidence for uric acid-lowering in people with tophaceous gout, radiographic damage due to gout, or frequent gout flares; some of whom also had CKD.[495]

The ERT assessed the safety of uric acid-lowering therapy and found that uric acid lowering did not increase adverse events among people with CKD, and particularly focused on risk of cutaneous reactions and hypersensitivity (pooled RR: 1.00; 95% CI: 0.60–1.65), and hepatotoxicity (pooled RR: 0.92; 95% CI: 0.37–2.30). Uric acid-lowering therapy was also found not to modify risk of cardiovascular events or all-cause mortality in people with CKD.[91, 497, 498] This reassuring cardiovascular safety profile is consistent with general population data. In the open-label Allopurinol and Cardiovascular Outcomes in Patients With Ischemic Heart Disease (ALL-HEART) randomized trial of 5721 people aged ≥60 years with ischemic heart disease but no history of gout. Allopurinol did not modify cardiovascular risk compared to standard care (hazard ratio [HR] for the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death: 1.04; 95% CI: 0.89–1.21). Findings were similar when the 540 people with an eGFR <60 ml/min per 1.73 m^2 at baseline

(among whom 71 primary outcomes accrued) were compared with the 5181 people with an eGFR of ≥60 ml/min per 1.73 m^2 (568 outcomes).[499]

Certainty of evidence

The overall certainty of the evidence for uric acid-lowering therapy among people with CKD and hyperuricemia is very low (see Supplementary Table S8). The critical outcome of delaying progression of CKD was addressed by 7 RCTs.[500-506] The 2 largest RCTs were considered to have a low risk of bias.[500, 501] The certainty of the evidence was downgraded for inconsistency because there was substantial statistical heterogeneity detected in the meta-analysis (I^2 = 50%) and the estimated relative risks ranged from 0.05 to 2.96. The certainty of the evidence was further downgraded because of very serious imprecision. There were 81 kidney failure events among the participants in the 7 trials.

The overall certainty of the evidence for delaying progression is very low and the certainty for the critical harm outcomes, cutaneous reactions and hypersensitivity and hepatotoxicity, was graded as low. However, the certainty of evidence for uric acid-lowering interventions in reducing frequency and severity of gout attack, and limiting tophaceous deposition is consistently high, so the recommendation is given an overall grade of Level C.

Values and preferences

People with gout have reported that they were initially hesitant to start uric acid-lowering therapy, but that after experiencing improved control of inflammatory symptoms and tophi, they became strong advocates for its earlier institution.[495]

Resource use and costs

There are several generic xanthine oxidase inhibitors which are well-tolerated and widely available at low cost.

Considerations for implementation

In most countries, the cost and availability of uric acid-lowering therapies make the medications very accessible. The risk of serious adverse events (e.g., Stevens Johnson syndrome) is related to the presence of specific HLA*B5801, which is more common in those of Asian descent. In specific regions, assessment of the HLA type is recommended prior to commencing the drug; where testing is not available, close monitoring at initiation of the medication should be undertaken. At the current time, there is no indication to commence medication for high serum uric acid levels in the absence of symptoms.

Rationale

Uric acid-lowering therapy reduces uric acid levels and their associated symptomatic joint and skin complications and are generally safe to use.

Practice Point 3.13.1: 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]).

Although initiation of uric acid-lowering therapy in people with a first gouty arthritis episode and no tophi was not recommended by the American College of Rheumatology, uric acid-lowering therapy use was suggested to be initiated in people with CKD G3–G5, serum uric acid concentration >9 mg/dl (535 µmol/l), or urolithiasis at the time of their first episode of gout. This was justified by the higher risk of gout progression and development of clinical tophi in CKD.[495] The ERT evidence review identified that uric acid-lowering therapy results in an increased risk of a gout flare during the first 3 months after initiation in people with CKD. This is an expected short-term risk of uric acid-lowering which people should be counselled about when initiating such therapy. Two relatively small randomized trials have suggested starting uric acid-lowering therapy during a gout flare does not appear to extend flare duration.[507, 508] Once initiated, the American College of Rheumatology suggest continuing uric acid-lowering therapy indefinitely.[495]

Practice Point 3.13.2: Xanthine oxidase inhibitors are preferred over uricosuric agents in people with CKD and symptomatic hyperuricemia.

Xanthine oxidase inhibitors (e.g., allopurinol and febuxostat) reduce serum uric acid concentration by reducing purine metabolism into uric acid. Uricosuric agents enhance its urinary excretion (probenecid is an example), but their effect is blunted in the context of reduced GFR. Note that the Cardiovascular Safety of Febuxostat and Allopurinol in Participants With Gout and Cardiovascular Comorbidities (CARES) double-blind randomized trial of allopurinol versus febuxostat in 6190 people with gout and prior CVD found that these 2 interventions were noninferior with respect to the composite primary cardiovascular outcome. However, mortality overall and cardiovascular mortality was higher in the febuxostat group than in the allopurinol group (HR for death from any cause: 1.22; 95% CI: 1.01–1.47 and HR for cardiovascular death: 1.34; 95% CI: 1.03–1.73).[509] In people with T2D, *post hoc* analyses from 2 large, placebo controlled RCTs have reported that SGLT2i reduce serum uric acid concentration and appeared to reduce gout adverse event reports or initiations of uric acid-lowering therapy.[410, 510] Observational studies suggest diuretics (thiazide and loop) increase serum uric acid concentration.[511] The effect is mediated through multiple potential kidney-centered mechanisms which are summarized in a review of drug-induced hyperuricemia.[512]

Practice Point 3.13.3: For symptomatic treatment of acute gout in CKD, low-dose colchicine or intra-articular/oral glucocorticoids are preferable to nonsteroidal anti-inflammatory drugs (NSAIDs).

The American College of Rheumatology recommended that colchicine, NSAIDs, or glucocorticoids are preferred first-line therapies for acute gout treatment based on demonstrated high levels of evidence for efficacy, low cost, and tolerability.[495]

Administration early after symptom onset is encouraged. For colchicine, the FDA-approved dosing (1.2 mg immediately followed by 0.6 mg an hour later, with ongoing anti-inflammatory therapy until the flare resolves) was highlighted.[495] Anti-inflammatory treatment may be useful as prophylaxis against a symptomatic flare when initiating uric acid-lowering therapy and may sometimes be required long-term (without diarrhea). We have advised that low-dose colchicine is preferable to NSAIDs given the safety and tolerability profile and may also reduce risk of cardiovascular events.[513] In contrast, NSAIDs can cause toxicity in CKD, and need to be used cautiously.[514] Short courses of glucocorticoids titrated to symptoms response (e.g., 30 mg prednisolone orally for 3–5 days) could be used as an alternative.

Dietary approaches

Practice Point 3.13.4: Nonpharmacological interventions which may help prevent gout include limiting alcohol, meats, and high-fructose corn syrup intake.

High alcohol intake high purine intake and consumption of carbonated drinks are associated with higher levels of serum uric acid. Consumption of these products in higher amounts is associated with both higher levels and gout symptoms. In contrast, diets that are low in fat and dairy, and high fiber, plant-based diets are associated with lower incidence of gout. Thus, diet modification may be of value in people with CKD, high uric acid, and gout.

Serum uric acid levels among people with a history of gout are higher in those with higher versus moderate levels of alcohol intake (≥30 units/week vs. <20 units per week); as is the risk of recurrence.[511, 515] The odds of gout also appear higher among those with higher median purine intake (≥850 mg vs. <850mg estimated purine intake in the last 24 hours).[511] Experimentally, 2 hours after ingestion of 1 g/kg of body weight of fructose, serum uric acid concentration increases by 1–2 mg/dl (59.5–119 µmol/l),[516] and its consumption in carbonated drinks is observationally associated with higher serum uric acid concentration levels,[517, 518] and incident gout (whereas diet versions of these drinks are not).[519] Foods associated with a low incidence of gout include low fat dairy, and high-fiber and plant-based diets.[520]

Special considerations

Pediatric considerations

There are no uric acid lowering trials in children.

International considerations

Asian (as opposed to African and Caucasian) ethnicities may be at higher risk of serious skin cutaneous reactions if they carry the *HLA-B*5801* allele. It has been suggested that *HLA-B*5801* allele screening may be considered in people who will be treated with allopurinol (although there is uncertainty that screening would be cost-effective).[521]

Recommendation 3.13.2: We suggest not using agents to lower serum uric acid in people with CKD and asymptomatic hyperuricemia to delay CKD progression (2D).

The Work Group judged that most well-informed people with CKD would prefer to optimize medical therapies that have proven benefit for CKD progression, and that the evidence does not support treatment of asymptomatic hyperuricemia to modify risk of CKD progression.

Key information

Balance of benefits and harms

On balance, despite observational studies implicating elevated serum uric acid levels in the progression of CKD, the data from systematic reviews and multiple RCTs do not support treatment in the absence of symptoms. Given the pill burden and lack of data, there is little support for use of uric acid-lowering agents. Observational data that implicate elevated serum uric acid levels in the progression of CKD have not been shown to reflect causal associations,[522, 523] as RCTs evaluating uric acid lowering on progression of CKD do not demonstrate clear benefit on progression, including data summarized in a Cochrane systematic review comprising 12 RCTs which had randomized 1187 participants.[497] Since the 2017 Cochrane review, 3 large and important RCTs with negative results have been conducted in people with CKD and asymptomatic hyperuricemia Table 31).[500, 501, 524]

The ERT review identified 25 studies (26 publications) that compared a uric acid-lowering therapy with placebo, usual care, or another uric acid-lowering therapy among people with CKD and hyperuricemia.[91, 500, 502, 505, 506, 509, 525-544] Twenty-two studies (23 publications) [91, 500, 509, 525-544] were new studies published since the Cochrane review or were not captured by the Cochrane 2017 review.[497] We did not include 9 studies from the Sampson *et al*. review because they did not include a separate analysis among people with CKD or because the study was reported as a meeting abstract only. Among people with CKD and hyperuricemia, the effects of uric acid-lowering therapy compared to placebo or usual care were unclear in terms of progression kidney failure (pooled RR: 0.92; 95% CI: 0.43–1.98 for studies ranged in follow-up from 3 months to 7 years), cutaneous reactions and hypersensitivity (pooled RR: 1.00; 95% CI: 0.60–1.65), and hepatotoxicity (pooled RR: 0.92; 95% CI: 0.37–2.30). Lastly, within the various therapies among people with CKD and hyperuricemia, the effects of febuxostat compared with benzbromarone on cutaneous reactions and hypersensitivity were unclear (RR: 0.20; 95% CI: 0.01–4.01).

Study N	CKD population	Intervention Follow-up	Outcome
CKD-FIX[500] N=369	CKD G3–G4, mean ACR 717 mg/g, mean urate 8.2 mg/dl	Allopurinol vs. placebo 104 weeks	No significant difference in eGFR decline (-3.33 vs. -3.23 ml/min per 1.73 m^2/yr
PERL Study Group[501] N=530	eGFR 40–99.9 ml/min per 1.73 m^2 and Type 1 diabetes	Allopurinol vs. placebo 3 years	No significant difference in mGFR decline, -3.0 vs. -2.5 ml/min per 1.73 m^2/yr
FEATHER Study[524] N=467	CKD G3	Feboxostat vs. placebo 108 weeks	No significant difference in eGFR slope 0.23 ± 5.26 vs. -0.47±4.4.8 ml/min per 1.73 m^2

Table 31. Randomized controlled trials in the treatment of asymptomatic hyperuricemia in people with chronic kidney disease (CKD). ACR, albumin-to-creatinine ratio; CKD-FIX, Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase; eGFR, estimated glomerular filtration rate; FEATHER, Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3;PERL, Preventing Early Renal Loss in Diabetes

Certainty of the evidence

The overall certainty of the evidence for uric acid-lowering therapy among people with CKD and hyperuricemia is very low. The critical outcome of delaying progression of CKD was addressed by 7 RCTs.[91, 500-502, 504-506] The certainty of the evidence was downgraded for inconsistency because there was some statistical heterogeneity detected in our meta-analysis (Supplementary Table S8). The certainty of the evidence was further downgraded because of very serious imprecision as there were few events in the trials.

Values and preferences

The Work Group judged that most well-informed people with CKD would prefer to optimize medical therapies that have proven benefit for CKD progression, and that there is little evidence to support treatment of asymptomatic hyperuricemia to modify risk of CKD progression.

Resource use and costs

There are no cost considerations, beyond cost-savings, in our recommendation not to use uric acid-lowering agents.

Considerations for implementation

There are no implementation considerations in our recommendation not to use uric acid-lowering agents.

Rationale

There is insufficient evidence to recommend the use of uric acid-lowering therapies in asymptomatic hyperuricemia for the specific purpose of delaying CKD progression. We make the recommendation not giving uric acid-lowering therapy in asymptomatic

hyperuricemia for slowing of kidney disease based on the current evidence that suggests unclear benefits. We judge that it is best practice not to expose people to medications that provide little benefit.

3.14. Cardiovascular disease (CVD) and additional specific interventions to modify risk

Prevalence and diagnosis

People with CKD are at increased risk of CVD,[545, 546] a key feature of which is structural heart disease, heart failure, and sudden death.[547-549] Increased risk of atherosclerotic disease also accompanies CKD.[545] These risks increase progressively as eGFR declines (Figure 31).[4] Risk of death from CVD exceeds risk of progression to kidney failure for the majority of people with CKD.

Figure 31. Risk of all-cause and cardiovascular mortality by estimated GFR (eGFR) and level of albuminuria from general population cohorts contributing to the Chronic Kidney Disease (CKD) Prognosis Consortium. ACR, albumin-to-creatinine ratio

The diagnosis of cardiac disease can be more complex and challenging in CKD, with many standard tests needing careful consideration in people with CKD.[550, 551] For example, exercise electrocardiography may be limited through inability to exercise to a diagnostic workload, or presence of microvascular disease. Perceived risks of contrast agents may limit the use of diagnostic imaging thus impacting treatment choices; risks of contrast agents may limit the use of imaging; a strain pattern may mask diagnostic ST depression, and acute coronary syndrome is less likely to present with classical ischemic symptoms and electrocardiographic changes than in the general population, instead often manifesting as heart failure symptoms or syncope.[550, 551] In people with GFR <60 ml/min per 1.73 m^2 (GFR categories G3a–G5), KDIGO has previously recommended that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome.[1] More sensitive troponin assays maintain high diagnostic accuracy in people with CKD, but higher assay-specific optimal cutoff levels may be considered.[552] Regardless of assay, careful attention to trends in troponin concentration over time is required through serial measurement.[553]

Management

In people with CKD, the same principles should be used to manage atherosclerotic risk as in people without CKD. The level of care for CVD offered to people with CKD should not be prejudiced by their GFR. Data suggest underuse of proven effective treatment in people with CKD presenting with acute coronary syndrome.[554]

Prevention of ASCVD should consider pharmaceutical, dietary, and lifestyle intervention which target traditional cardiovascular risk factors (e.g., BP and dyslipidemias) as well as CKD-MBD which accelerates vascular calcification resulting in both vascular intima (resulting in increased amounts of calcium in atherosclerotic plaques[555]) and vascular media calcification (leading to increased vascular stiffness).[492]

3.14.1 Lipid management

Dyslipidemia in CKD is frequently characterized by high triglycerides, low high-density lipoprotein (HDL) cholesterol, and an increased proportion of low-density lipoprotein (LDL) particles which are small and oxidized.[556] In adults with newly identified CKD, it has been recommended to evaluate their lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), but follow-up lipid measurements are not required for the majority of people (i.e., a fire-and-forget policy is recommended).[15] This is because treatment initiation is based on risk and the benefits of statin-based therapy have been shown to be independent of level of cholesterol. For those with a total cholesterol >7.5 mmol/l (290 mg/dl) and a personal or family history of premature ischemic heart disease (e.g., an event before the age of 60 years in an individual or first-degree relative), it is important to consider familial disease and specialist referral.[557]

The benefits of lowering LDL cholesterol using statin-based therapies on risk of ASCVD 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*.[15] The Work Group concurs with all the recommendations in this guideline. In particular, we draw attention to:

Recommendation 3.14.1.1: 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 3.14.1.2: 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 3.14.1.3: 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**
- **estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%**

The Work Group offer the following practice points to support implementation of the recommendations above.

Practice Point 3.14.1.1 Estimate 10-year cardiovascular risk using a validated risk tool.

Details of the Work Group recommendations on how to estimate risk are provided in Chapter 2, Section 2.3. As of the writing of this guideline, the CKD patch for the Systematic Coronary Risk Evaluation (SCORE) tool is the only one validated

Practice Point 3.14.1.2: 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.

Since 2013, published literature has continued to demonstrate the general safety of statin-based therapies.[558] This includes individual participant level data meta-analysis by the Cholesterol Treatment Trialists' collaboration showing that statin therapy causes only a small excess of mild muscle pain with most (>90%) of all reports of muscle symptoms among users not due to their statins.[559] In CKD, the Study of Heart and Renal Protection (SHARP) demonstrated that an intensive statin-based regimen was safe and not associated with any serious nonvascular hazard.[560, 561] A Cholesterol Treatment Trialists' collaboration meta-analysis combining SHARP with the other large trials took into account the smaller reductions in LDL cholesterol achieved with statin-based therapy in people with CKD G3–G5. After standardization to a 1.0 mmol/l (38.7 mg/dl) LDL cholesterol difference, the relative risk reductions in major vascular events observed with statin-based treatment in the large statin trials were shown to become progressively smaller as eGFR declines, with little evidence of benefit in people on dialysis (Figure 32).[562] The corollary of this observation is that in people with CKD, statin-based regimens should be chosen to maximize the absolute

reduction in LDL cholesterol to achieve the largest treatment benefits. Large trials have shown the following once daily intensive statin-based regimens are safe in CKD (including people on dialysis): atorvastatin 20 mg;[563] rosuvastatin 10 mg;[564] and simvastatin 20 mg combined with ezetimibe 10 mg.[560, 561]

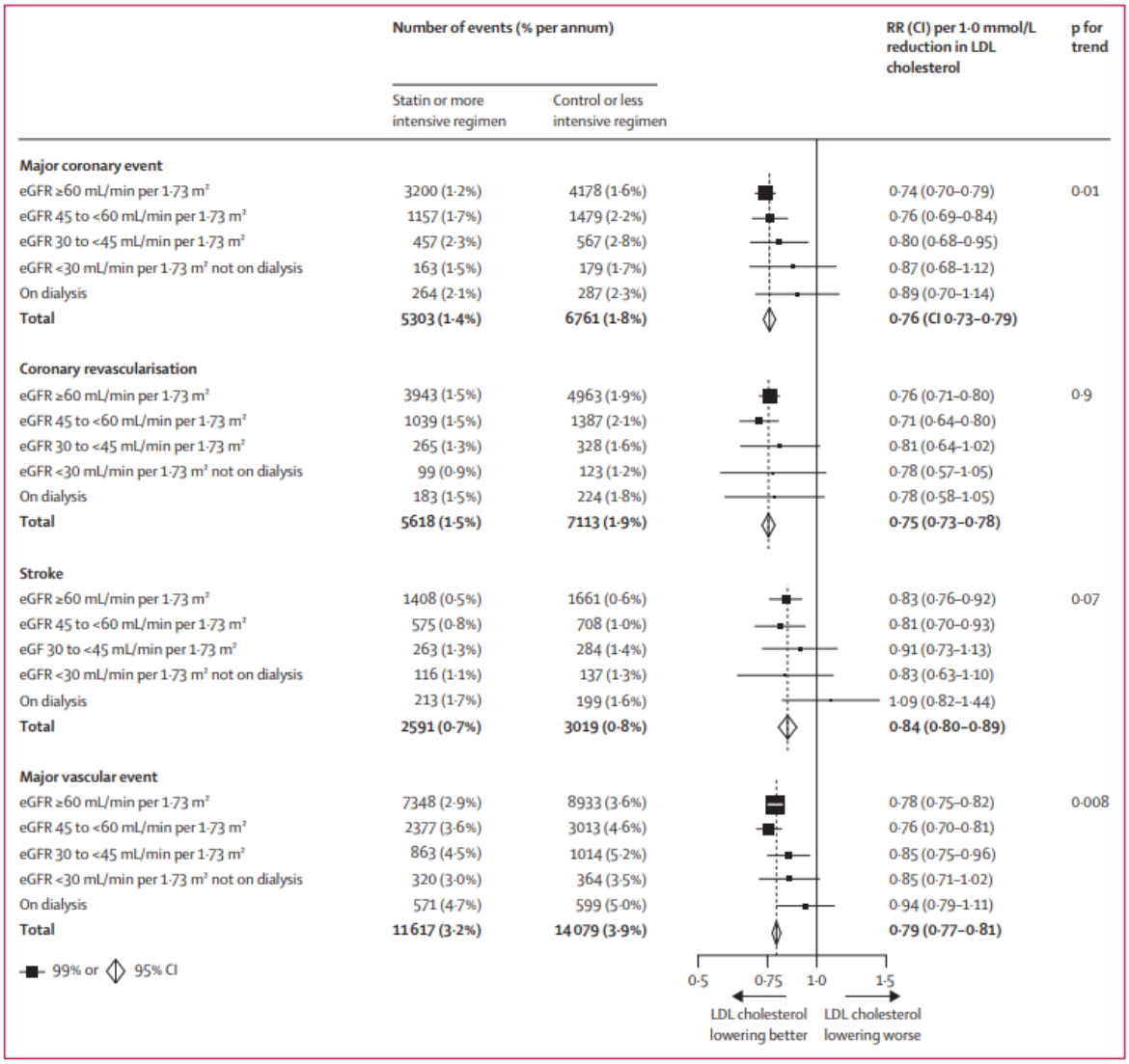


Figure 32. Effect of lowering low-density lipoprotein (LDL) cholesterol per 1.0 mmol/l on risk of major vascular events by level of estimate glomerular filtration rate (eGFR) at recruitment. CI, confidence interval; RR, relative risk. Meta-analysis of 28 large trials of statin-based therapy using individual participant level data. Black squares and horizontal lines represent 99% confidence intervals, with diamonds representing 95% CI. Reproduced from Cholesterol Treatment Trialists' Collaboration. Lancet Diabetes & Endocrinology Figure 1.[565]

Practice Point 3.14.1.3: Consider prescribing proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors to people with CKD who have an indication for their use.

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have been show to safely reduce ASCVD risk when added to maximal tolerated statin-based regimens in people at high coronary risk.[566, 567] Subgroup analyses suggest their safety profile and their biochemical and clinical efficacy are similar when participants with CKD and without CKD are compared. These trials recruited down to an eGFR of 20 ml/min per 1.73 m^2.[568, 569]

Dietary approaches

Practice Point 3.14.1.4: Consider a plant-based "Mediterranean-style" diet in addition to lipid-modifying therapy to reduce cardiovascular risk.

Diet and lipids have been comprehensively reviewed by other clinical practice guidelines.[570, 571] In that work, the Work Groups highlighted that in general populations, observational studies have associated plant-based diets that include higher consumption of fruit, vegetables, nuts, legumes, fish, olive oil, yogurt, and whole grains with lower risk of cardiovascular disease. Diets associated with higher risk are those including high consumption of red and processed meats, refined carbohydrates, and salt. Vegetable sources of fats and polyunsaturated fatty acids (e.g., in nuts, seeds, avocado and olive oil) are also associated with lower risk than animal fats, including dairy fat.[570] A Mediterranean-style diet has an emphasis on extra-virgin olive oil and is high in unsaturated fat. RCTs have shown such diets have important effects on cardiovascular risk in the long-term despite only small effects on traditional markers of metabolic syndrome profile.[572-575] In the large Prevención con Dieta Mediterránea (PREDIMED) primary prevention trial of 7447 adults, the Mediterranean diet rich in extra virgin olive oil reduced the risk of major cardiovascular events by 31% (HR: 0.69; 95% CI: 0.53–0.91). The Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention (CORDIOPREV) trial found that allocation to a Mediterranean diet rich in extra virgin olive oil reduced the risk of the composite of MACE by about 22%–25%.[574] There is no large-scale CKD-specific trial comparing these dietary interventions.

3.14.2. Use of antiplatelet therapy

Recommendation 3.14.2.1: 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).

This recommendation places high value on the importance of reducing recurrence of myocardial infarction, ischemic strokes, or peripheral arterial disease complications in people with CKD and established ischemic CVD due to the mortality and disability associated with such complications. In secondary prevention, trials have clearly shown the absolute benefits of low-dose aspirin substantially exceed the potential for bleeding complications creating certainty about net benefits when treating this population. In people with CKD without prior ischemic CVD, the balance of benefits and risks are uncertain and may be counterbalanced – large RCTs are ongoing.

Key information

Balance of benefits and harm

Based on a number of large RCTs in populations which are likely to be largely free from CKD, lifelong use of low dose aspirin (75–100 mg) for prevention of recurrence of complications of ischemic CVD is strongly recommended among people with known CVD (a therapeutic approach referred to as secondary prevention). Conversely, it is not possible to provide definitive recommendations on when to use aspirin to prevent a first ischemic cardiovascular event (i.e., primary prevention) in people at high risk, and a research recommendation is provided. This is due to uncertainty of the net absolute value of such an approach, as any reduction in the risk of atherosclerotic cardiovascular events needs to be weighed against the risk of major bleeding. It is important to consider CKD-specific data in the totality of the evidence.

Key evidence from general populations is derived from a 2009 meta-analysis by the Anti-thrombotic Treatment Trialists' collaboration. The analyses included data on long-term aspirin use versus control care in 16 secondary prevention trials (~17,000 people at high average risk, ~43,000 person-years, 3306 serious vascular events [defined as myocardial infarction, stroke, or cardiovascular death]), and 6 primary prevention trials (~95,000 participants at low average risk, ~660,000 person-years, 3554 serious vascular events).[576] In the secondary prevention trials, allocation to aspirin reduced the risk of both ischemic stroke and myocardial infarction by about one-fifth, such that overall relative risk reduction for any serious vascular event was by 19% compared to controls (relative risk [RR]: 0.81; 95% CI: 0.75–0.87). This equated to a 1.49% per year lower absolute risk of serious vascular events compared to an estimated absolute risk of any major bleeding which was an order of magnitude smaller at 0.03% per year. Note that this hazard of major bleeding was extrapolated from the primary prevention trials as stroke causes and extracranial bleeds were generally not well recorded in the relatively older secondary prevention trials (Figure 33).

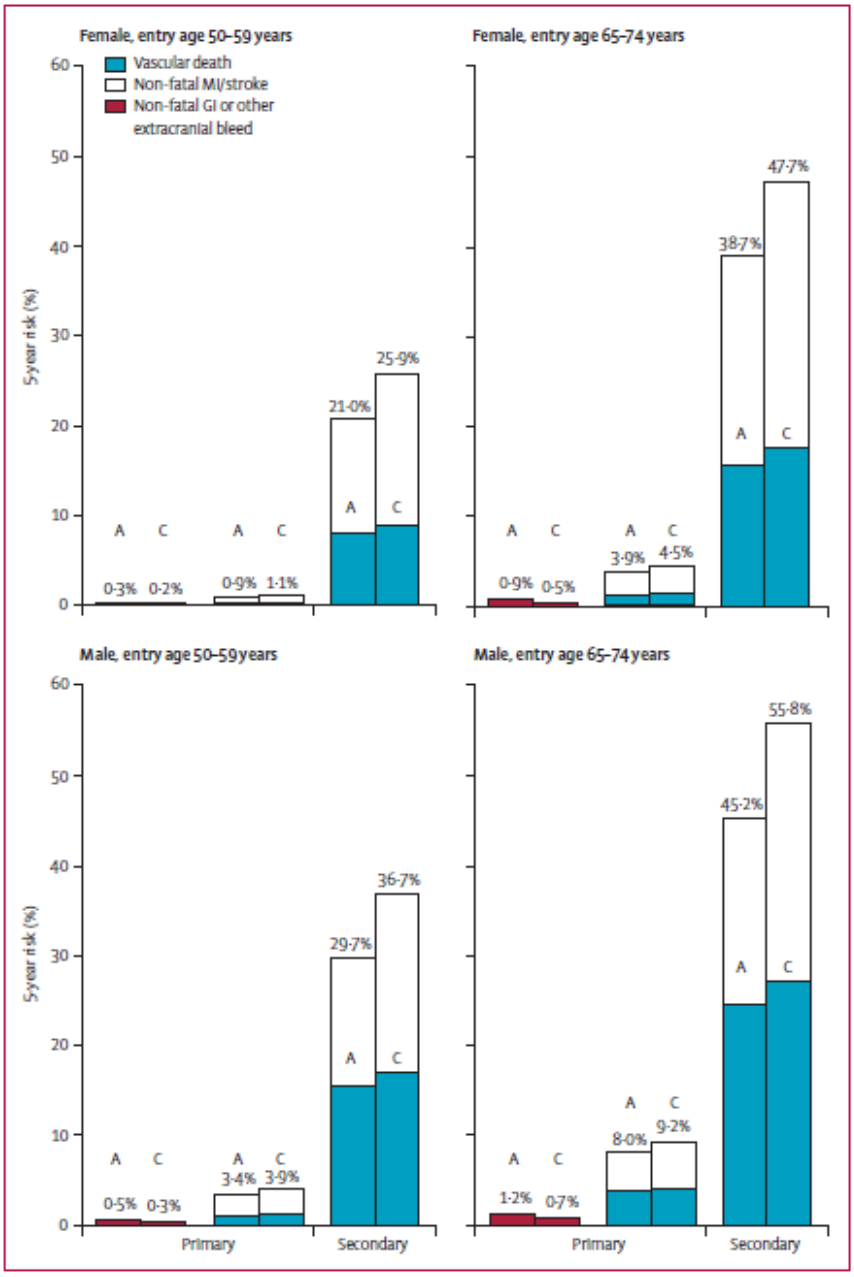


Figure 33. Predicted 5-year absolute benefits and harms of allocation to aspirin (A) versus control (C) using a secondary or primary prevention strategy, by different levels of risk (based on age and sex). GI, gastrointestinal; MI, myocardial infarction. Adapted from: Antithrombotic Treatment Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet Figure 6.[576]

Some people with CKD have been included in antiplatelet therapy trials. A recent Cochrane collaboration meta-analysis of 40,597 trial participants with CKD recruited into antiplatelet versus placebo trials, and 11,805 recruited into antiplatelet agent comparison trials found that allocation to antiplatelet therapy may reduce the relative risk of myocardial infarction by about 12% (RR: 0.88; 95% CI: 0.79–0.99). There was an expected increased risk of major bleeding, but the magnitude of the relative risk was consistent with the data from general populations (RR: 1.35; 95% CI: 1.10–1.65).[577] Note that these analyses did not

distinguish between primary and secondary prevention settings.[577] The 2009 Anti-thrombotic Treatment Trialists' collaboration meta-and results from 3 more recent large trials (A Study of Cardiovascular Events in Diabetes [ASCEND],[578] Aspirin in Reducing Events in the Elderly [ASPREE],[579] and Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE][580]) assessing the effects of aspirin versus placebo for primary prevention in specific high risk populations found any harm from major bleeding counterbalanced any benefit of aspirin on cardiovascular risk (with ASPREE and ARRIVE both finding no significant effect on cardiovascular events in their studied populations of older adults or high risk adults respectively).[576] A dedicated large primary prevention aspirin trial in CKD is underway.[581]

Certainty of evidence

The 2009 meta-analysis by the Anti-thrombotic Treatment Trialists' collaboration on the effect of aspirin compared to placebo in terms of the primary and secondary prevention of CVD and safety among people with and without CKD was assessed to have high risk of bias using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) checklist due to unclear identification and selection of studies, unclear data collection and study appraisal, and high risk of bias for synthesis and findings (although we did not contact the authors to clarify these details).[576] This review did not report on the evidence or certainty of evidence assessments directly in the report. Given the available evidence, the recommendation has a low certainty of evidence (Level C).

Value and preferences

Maintaining QoL by minimizing risk of worsening of ischemic heart disease and recurrent stroke-related disability is important to both people with CKD and caregivers.[582] The Work Group considered the risk of bleeding would be considered acceptable by most people with CKD once the clear net benefits were explained and gastroprotection was offered. The Work Group considered that some people with CKD without prior ischemic coronary, cerebrovascular, or peripheral arterial disease but at increased risk (e.g., due to diabetes) may still wish to consider using aspirin and accept the risk of major bleeding.[578] Some people with CKD may also have a kidney diagnosis which indirectly supports considering use of aspirin despite a lack of evidence (e.g., presumed or proven renovascular disease). The Work Group are not aware of any risk tools that could be used to help counsel such people with CKD as to their expected net absolute benefits and risks based on risk factors of the person with CKD, including any difference by sex. (Note that scores to predict cardiovascular risk are considered in Chapter 2).

Resource use and costs

Low-dose aspirin is available at low cost and does not require monitoring.

Considerations for implementation

Proton pump inhibitors are generally effective,[583] safe, and low cost (although occasionally associated with an interstitial nephritis), and the Work Group consider that it is prudent to consider bleeding risk and offer proton pump inhibitors when prescribing

antiplatelet therapy or antithrombotic therapy, particularly when such therapies are combined.[584]

Rationale

Meta-analysis of trials has clearly established the cardiovascular benefits of low-dose aspirin in people who have established ASCVD. Any harm of bleeding is far outweighed by the benefits (unlike the situation for primary prevention, where bleeding risk has been consistently identified in large aspirin trials and cardiovascular benefits to date have not).

Practice Point 3.14.2.1: Consider other antiplatelet therapy (e.g., $P2Y_{12}$ inhibitors) when there is aspirin intolerance.

Bleeding from gastrointestinal mucosa with antiplatelet therapy is likely to be due to their effect on hemostasis of preexisting mucosal lesions, which is further supported by the fact that use of $P2Y_{12}$ inhibitors (e.g., clopidogrel or ticagrelor) does not reduce the risk of bleeding in trials comparing them to aspirin. This hypothesis is supported by $P2Y_{12}$ inhibitors (e.g., clopidogrel or ticagrelor) not reducing risk of bleeding in trials comparing them to aspirin.[585, 586] However, if people are aspirin intolerant, a $P2Y_{12}$ inhibitor is a noninferior alternative. Note that in 2009, the US Food and Drug Administration (FDA) recommended that the coadministration of clopidogrel and omeprazole (a proton pump inhibitor) should be avoided because omeprazole reduces the effectiveness of clopidogrel. There is uncertainty about the precise effect of omeprazole as pharmacokinetic data are inconclusive, but proton pump inhibitors with inhibition of CYP2C19 are preferred when using clopidogrel.[587]

Guidelines from the cardiology community provide recommendations for use of dual antiplatelet therapy for a period after acute coronary syndrome or percutaneous coronary intervention. These guidelines recommend to apply the same diagnostic and therapeutic strategies in people with CKD.[588] CKD does not modify the benefits of ticagrelor[589] and antiplatelet therapy doses do not need to be modified at decreased eGFR. Note that other antithrombotic therapy choices and doses may need to consider a person's GFR.

Special considerations

International considerations

Given the clinical effectiveness of low-dose aspirin and its low cost, there should not be many barriers to accessing this medication in any setting.

3.14.3. Invasive versus intensive medical therapy for coronary artery disease

Recommendation 3.14.3.1: 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).

This recommendation places high value on the finding from recent, large trials in both general and CKD populations which have suggested intensive medical therapy is a suitable initial strategy for the management of stable stress-test confirmed ischemic heart disease. It places value on the need for interventions which carry risk to people with CKD and substantial healthcare costs to demonstrate benefits on cardiovascular outcomes before they are considered a standard of care. Importantly, this recommendation should not apply to those with severe angina symptoms, left ventricular dysfunction (e.g., ejection fraction <35%), or left main stem disease as they were excluded from the definitive trials. It should be noted that trials in CKD have not ruled out antianginal benefits in people with CKD (despite negative findings).

Key information

Balance of benefits and harm

Benefits

Benefits should be considered in the context of the totality of evidence in people with and without CKD regarding interventions. Comparisons between aggressive medical therapy alone and invasive interventions do not support invasive strategies to reduce death, or prevent myocardial infarction[498,499]. However, those with frequent angina symptoms (at least weekly) gained improvement with the invasive strategy[498]; thus, the benefit of an invasive strategy might be restricted to those with angina. The reason for a lack of clear antianginal effect of an invasive strategy in International Study of Comparative Health Effectiveness with Medical and Invasive Approaches—Chronic Kidney Disease (ISCHEMIA-CKD) needs some consideration, and key reasons relating to insufficient power due to protocol differences have been are proposed.[590] Although low power to detect an effect on angina is a key potential explanation for differences in findings between the 2 trials, CKD-MBD and coronary calcification in CKD, which makes microvascular disease more common and increases the technical challenge of revascularization, may also have partly contributed.[591]

The ERT assessed the effects of angiography or coronary intervention in people with CKD and ischemic heart disease identified 4 other trials, but excluded mixed populations including ISCHEMIA-CKD which recruited some people on dialysis and some people who have received a kidney transplant. The review found no clear benefits on cardiovascular outcomes in 3 other trials and raised a hypothesis about beneficial effects on mortality overall (Supplementary Table S9). Such an effect has not been observed in the larger general population trials.

Harms

The harms of invasive strategies include risk of dialysis initiation, death, and stroke risk (stroke was interestingly not peri-procedure)[498].

Certainty of evidence

The ERT review was limited to trials only recruiting people with CKD (and did not include the ISCHEMIA-CKD trial discussed above due to the inclusion of some people on dialysis and some people who have received a kidney transplant). The overall certainty of the evidence comparing coronary revascularization with optimal medical therapy among people with CKD not undergoing KRT and ischemic heart disease is very low (Supplementary Table S9). Most of the RCTs reporting on the critical outcomes (all-cause mortality, CVD mortality, CVD events, kidney failure, and AKI) had some concerns regarding the risk of bias, particularly with lack of blinding for the outcome assessors, participants crossing over to the other treatment group, and the selection of reporting. The certainty of the evidence was downgraded for all outcomes because of imprecision. The certainty of the evidence for cardiovascular mortality was downgraded because publication bias was strongly suspected.

Value and preferences

Although this was not confirmed by ISCHEMIA-CKD, antianginal benefits of an invasive strategy are apparent in general populations, and people with symptoms may still elect for an initially invasive approach to manage stable stress test confirmed coronary artery disease after being counselled about the risks.

Resource use and costs

It is not possible to formally assess the cost-effectiveness of intensive medical therapy versus an initial invasive strategy due to mixed findings from the evidence in people with stable ischemic heart disease. However, invasive strategies will have higher cost implications to healthcare systema, people with CKD, or both.

Considerations for implementation

Access and availability of invasive therapies will vary in different healthcare systems, as might the availability of medications for maximal medical therapy. The key to implementation is to encourage understanding of the value of full therapy as compared to invasive therapy so that healthcare providers and people with CKD understand the risks and benefits of invasive strategies. Given the costs of invasive strategies, there may be additional value to implementing this recommendation.

Rationale

Evidence suggests that the key indication for an initial invasive strategy to manage stable ischemic heart disease is based on symptoms, and intensive medical therapy is a suitable approach if symptom control is satisfactory in people with or without CKD. In CKD, the antianginal benefits of an initially invasive approach have not been demonstrated.

Practice Point 3.14.3.1: Initial management with an intensive 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.

The ISCHEMIA trial has been described as deeply disrupting prior attitudes regarding management strategies for people with stable coronary artery disease,[592] and clinical practice guidelines which predate the trial need updating.[593] Despite the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) and ISCHEMIA-CKD trial results, it is considered that the well-established intervention of coronary revascularization will continue to have a key role in angina relief.[592] Importantly, this recommendation should not apply to those with unacceptably severe angina symptoms. It should also be noted that people with left ventricular dysfunction (i.e., ejection fraction <35%), or left main disease were excluded from the definitive ISCHEMIA trial.[594] The Work Group considers certain design features of the ISCHEMIA-CKD trial may have led to angina benefits not being detected, and the trial results should not rule out angina benefits in people with CKD (see above). If an invasive strategy is pursued, there are effective strategies to reduce risk of contrast-induced AKI (Chapter 4).[595]

The totality of the evidence from the CKD-specific trials is consistent with no net difference between an initial conservative approach using aggressive medical therapy versus an invasive strategy when treating stable stress-test confirmed ischemic heart disease. This is consistent the large general population-based ISCHEMIA trial.[594]

3.15. CKD and atrial fibrillation

In CKD, the same principles to diagnose and manage atrial fibrillation should be used as in people without CKD.

Prevalence and consequences

Atrial fibrillation is the commonest sustained arrhythmia, with risk increasing steeply with increasing age (earlier in men than women).[596] There is a particularly high prevalence in people with CKD. Crude prevalence ranging from 16%–21% have been reported in people with CKD not requiring KRT.[61] In the cohorts contributing to the CKD-PC, adults with CKD G3, A1 had an adjusted risk of atrial fibrillation of 1.2–1.5 increasing to adjusted risks of 4.2 by CKD stages G5, A3 (Figure 34).

Figure 34. Meta-analyzed adjusted prevalence of atrial fibrillation from cohorts contributing to the Chronic Kidney Disease (CKD) Prognosis Consortium, by diabetes status. ACR, albumin-to-creatine ratio

Atrial fibrillation can directly cause thromboembolism (particularly stroke) and/or heart failure. It is also linked, perhaps directly or through shared risk factors, with increased risk of death, hospitalization, vascular dementia, depression, and reduced QoL.[596] Detailed clinical practice guidelines have been formulated by the cardiology community describing definitions, classification, diagnosis, screening strategies, and management.[596] It is beyond the scope of this KDIGO guideline to consider all aspects of the diagnosis and management of atrial fibrillation in people with CKD. The ERT review focused on the role of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin for thromboprophylaxis in CKD.

Identification and management

Atrial fibrillation can be asymptomatic but symptoms are not a prerequisite for risk of complications. As the prevalence of atrial fibrillation is high in people with CKD and there are effective strategies to manage its associated complications, opportunistic pulse-based screening (e.g., when taking BP), followed by a 12-lead electrocardiogram (ECG) if an irregularly irregular pulse is identified should be considered. Such an approach is low cost and simple to implement. Figure 35 outlines approaches to different diagnostic and management strategies.

Practice Point 3.15.1: Follow established strategies for the diagnosis and management of atrial fibrillation (Figure 35).

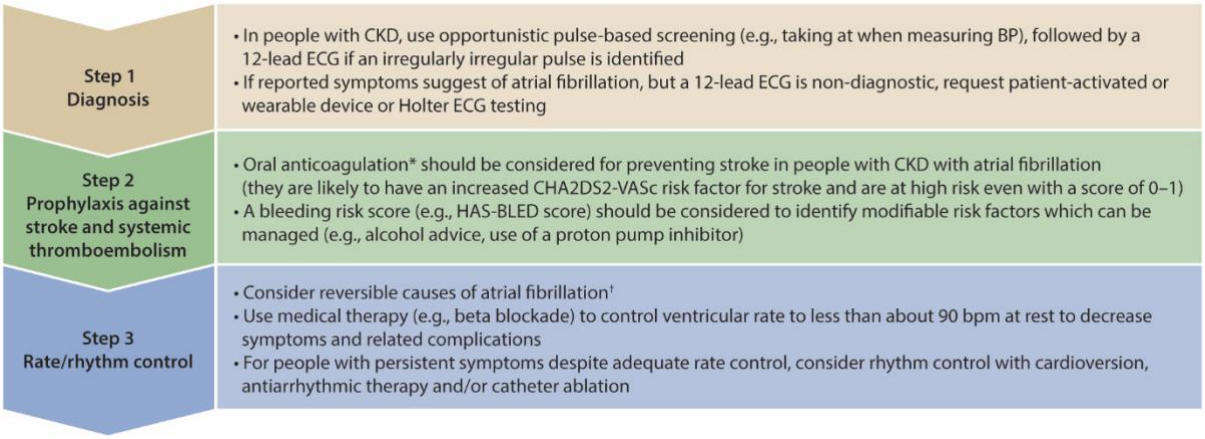


Figure 35. Strategies for the diagnosis and management of atrial fibrillation. *Consider dose adjustments necessary in people with CKD. †The following has been recommended as a standard package for diagnostic evaluation of new atrial fibrillation: (i) a 12-lead electrocardiogram (ECG) to establish the diagnosis, assess ventricular rate, and check for the presence of conduction defects, ischemia, or structural heart disease; (ii) laboratory testing for thyroid and kidney function, serum electrolytes, and full blood count; and (iii) transthoracic echocardiography to assess left ventricular size and function, left atrial size, for valvular disease, and right heart size and function. BP, blood pressure; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, and Sex category (female); CKD, chronic kidney disease; HAS-BLED, Hypertension, Abnormal liver/kidney function, Stroke history, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly, Drug/alcohol usage.

Prophylaxis against stroke and systemic thromboembolism

Recent cardiology guidelines recommend a risk factor-based approach to stroke thromboprophylaxis decisions in atrial fibrillation using the Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, and Sex category (female) (CHA_2DS_2-VASc) stroke risk score. They recommend that only people at "low stroke risk" (CHA_2DS_2-VASc score = 0 in men, or 1 in women) should not be offered antithrombotic therapy. Oral anticoagulants should be considered for stroke prevention with a CHA_2DS_2-VASc score of 1 in men or 2 in women, considering net clinical benefit and values and preferences of people with CKD. Oral anticoagulants are clearly recommended for stroke prevention in people with atrial fibrillation and a CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[596] Our Work Group considered that oral anticoagulation for thromboprophylaxis should nearly always be considered for preventing stroke in people with decreased eGFR and atrial fibrillation (Figure 35). The presence of decreased GFR is a risk for thromboembolic stroke in people with atrial fibrillation.[61, 597, 598] It has been estimated that about 95% of people with an eGFR <60 ml/min per 1.73 m^2 have a CHA_2DS_2-VASc score of ≥2, increasing to ~99% at an eGFR <30 ml/min per 1.73 m^2.[597] Importantly, it has also been shown that in a group of people with a CHA_2DS_2-VASc score of 0 to 1 point (i.e., a group where thromboprophylaxis may not be considered indicated), people with CKD within the

group are at much higher risk of cerebrovascular and other systemic thromboembolic events, with an annual rate of 2.9% compared to 0.2% in people without CKD.[597]

Including GFR into atrial fibrillation risk scores has not shown important incremental benefit to its introduction (e.g., adding 2 points for creatinine clearance <60 ml/min to $CHADS_2$ - referred to as Renal Dysfunction, Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack [R_2CHADS_2]) - improved net reclassification index but not the C-statistic.[61] However, as decreased GFR is associated with age, diabetes, CVD, etc., so incremental predictive advantage by adding a CKD parameter to the CHA_2DS_2-VASc score which includes these parameter already would be expected to have little effect. There is considerable scope to improve the predictive performance of thromboprophylaxis risk scores for use in CKD.[599]

Recommendation 3.15.1: 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).

This recommendation puts high value on the use of NOACs, also referred to as direct-acting oral anticoagulants (DOACs), in people with CKD due to their simpler pharmacokinetic profile, dosing, and monitoring than vitamin K antagonists and due to their improved efficacy and relatively similar safety profile. Although people with CKD stages G4–G5 have been understudied in RCTs, implementation in such groups can be achieved after considering choice of NOAC and dosing.

Key information

Balance of benefits and harms

Benefits

Data from 42,411 participants who received NOACs and 29,272 participants who received warfarin in 4 phase III trials were meta-analyzed in 2014. Such trials largely excluded people with CKD G4–G5 but did include large numbers of participants with earlier stages of CKD. Overall, NOACs significantly reduced the risk of stroke or systemic embolic events by 19% compared with warfarin (RR: 0.81; 95% CI: 0.73–0.91). This benefit was a result largely from reduced risk of hemorrhagic strokes (RR: 0.49; 95% CI: 0.38–0.64). There were large amounts of data on stroke in those with a creatinine clearance <50 ml/min, and the relative benefits were consistent and clearly evident in people with CKD. There were also consistent effects in subgroup analyses by age, sex, prior diabetes, prior stroke, and $CHADS_2$ score.[600] A more recent meta-analysis published in 2021 only focused on subgroups with CKD and included data from 7 trials of NOACs versus warfarin in atrial fibrillation. It also reported a 19% reduced risk of stroke/thromboembolic complications in the NOAC group (HR: 0.81; 95% CI: 0.69–0.97).[601] Data in CKD G5 on dialysis were limited to observational studies.[601] Our evidence review aimed to collect information on subtypes of outcome from subgroups analyses reporting results specifically in people with CKD. Evidence of efficacy in the large trials is mainly for the outcomes of stroke and hemorrhagic stroke, but our review only found data from 3 trials for these outcomes resulting in imprecise estimates of effect.

The findings were qualitatively consistent with the totality of the evidence (Figure 36, Supplementary Table S10).

Figure 36. Pooled hazard ratio (HR) comparing non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin among people with CKD in terms of stroke. CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate

Harms

The 2014 meta-analysis of 4 large phase III trials found that NOACs reduced risk death from any cause by 10% confirming net safety (RR: 0.90; 95% CI: 0.85–0.95). Compared to warfarin, NOACs reduced risk of intracranial hemorrhage (defined as hemorrhagic stroke, epidural, subdural, and subarachnoid hemorrhage) by about one-half (RR: 0.48; 95% CI: 0.39–0.59) and risk of gastrointestinal bleeding was increased by about one-quarter (RR: 1.25; 95% CI: 1.01–1.55). Overall, there was no clear effect on the combination of these 2 safety outcomes referred to as major bleeding (RR: 0.86; 95% CI: 0.73–1.00).[600] There were large amounts of data on major bleeding in those with a creatinine clearance <50 ml/min, so reassuring safety data clearly extended to people with CKD. There were also consistent safety data in subgroup analyses by age, sex, prior diabetes, prior stroke, and $CHADS_2$ score. There was a suggestion that major bleeding was significantly reduced in people attending centers where time in therapeutic INR range was <66% compared to centers with ≥66% time in range (interaction p=0.02). This suggests that benefits of NOACs are in part a result of their simpler pharmacokinetic profile and dosing.[600] The 2021 meta-analysis which focused on CKD subgroups from 7 trials found bleeding events were also not significantly different among those allocated NOACs versus warfarin (HR: 0.83; 95% CI: 0.58–1.18).[601] Data in CKD G5 on dialysis were limited to observational studies.[601] Our evidence review was again limited to a small number of studies reporting subtypes of bleeding outcomes, and so analyses found imprecise estimates of treatment effect. The findings were qualitatively consistent with the totality of the evidence (Figure 37, Supplementary Table S11). The review raised a hypothesis that some NOACs may be more likely to reduce the risk of bleeding. However, given the evidence of effect modification by

time in therapeutic range in the warfarin group, we have not provided specific recommendations to prefer certain NOACs.

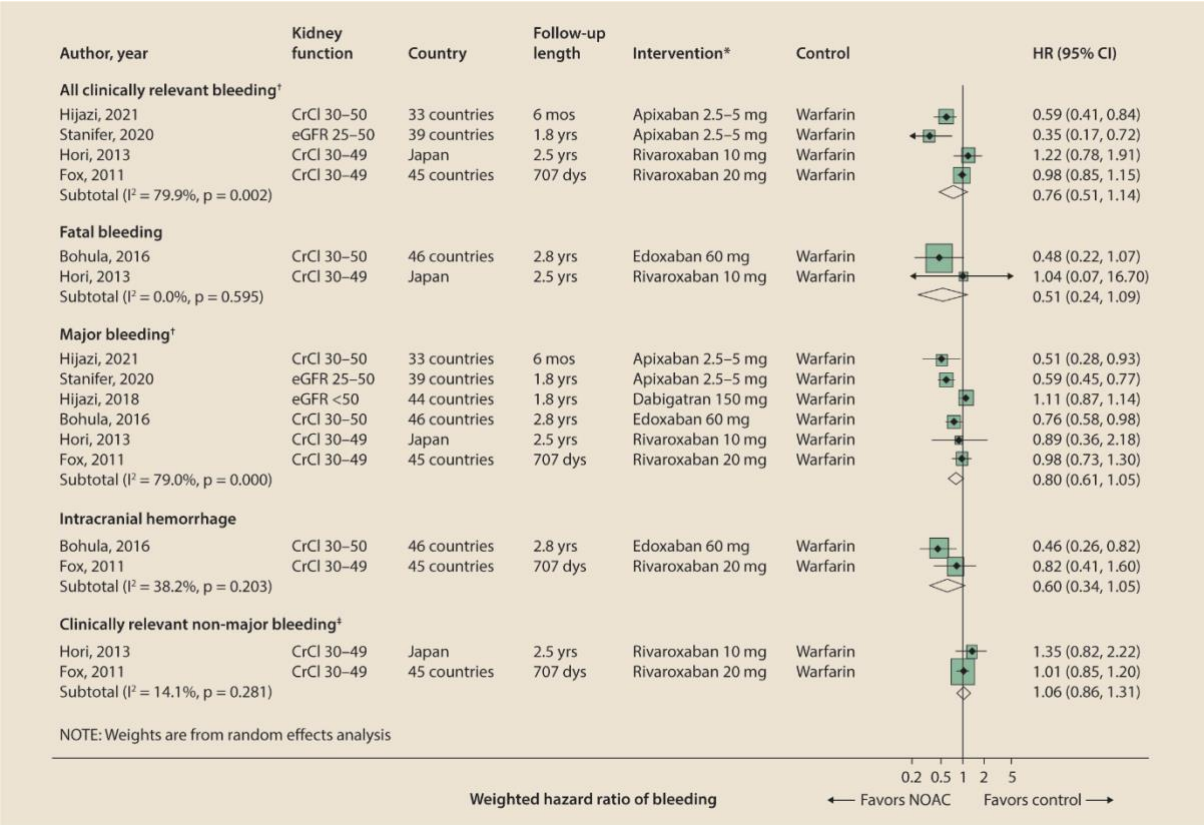


Figure 37. Pooled hazard ratio (HR) comparing non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin among people with chronic kidney disease (CKD) in terms of bleeding. CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate

Certainty of evidence

The overall certainty of the evidence comparing NOACs with warfarin among people with CKD and atrial fibrillation is low (Supplementary Tables S10 and S11). Most of the RCTs evaluating the critical outcomes were considered to have a low risk of bias. The critical outcome of stroke was reported as any stroke, ischemic stroke, and/or hemorrhagic stroke. Because there were few stroke events reported across the RCTs, the certainty of the evidence was downgraded for imprecision.

Value and preferences

High value on the use of NOACs included the conclusion that the simple dosing and lack of INR monitoring compared to vitamin K antagonists would lead to a substantial reduction in burden for those with an indication for anticoagulation and their health services. There is also good evidence for improved efficacy and a relatively similar safety profile. Most fully informed people with CKD would be expected to select a NOAC over a vitamin K antagonist.

Resource use and costs

NOACs have been shown to be cost-effective for stroke prevention in atrial fibrillation and may even be cost-saving in people with CKD. Vitamin K antagonist use may be associated with higher costs and achieve fewer quality-adjusted life years compared to NOACs.[602]

Considerations for implementation

A decision not to anticoagulate for thromboembolic prophylaxis due to low risk would ideally be reevaluated at each consultation and at least every 6 months. When using antithrombotic therapy in people with CKD, it is prudent to treat modifiable risk factors for bleeding (e.g., alcohol intake) and use gastroprophylaxis with a proton pump inhibitor, particularly when combined with antiplatelet therapy.

Rationale

A number of large RCTs demonstrated that NOACs reduce risk of intracranial bleeding compared to warfarin and overall, modestly reduce mortality in people with atrial fibrillation. They offer benefits in terms of ease of monitoring. CKD does not appear to importantly modify these benefits, at least down to G4.

Practice Point 3.15.2: NOAC dose adjustment for GFR is required, with caution needed at CKD G4–G5.

Doses of NOACs may need to be modified in people with decreased GFR taking into consideration a person with CKD's age, weight, and GFR (Figure 38). Consult relevant summaries of product characteristics for latest information on dosing (Chapter 4).

a

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban[c]	Rivaroxaban
>95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg QD[d]	20 mg QD
51–95	Adjusted dose (INR 2–3)	5 mg b.i.d.	150 mg b.i.d.	60 mg QD	20 mg QD
31–50	Adjusted dose (INR 2–3)	5 mg b.i.d. (eCrCl cut-off 25 mL/min)	150 mg b.i.d. or 110 mg b.i.d.[e]	30 mg QD	15 mg QD

b

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban	Rivaroxaban
15–30	Adjusted dose for INR 2–3 could be considered	2.5 mg PO b.i.d. could be considered	Unknown (75 mg PO b.i.d.)[f,g]	30 mg QD[e] could be considered	15 mg QD could be considered
<15 not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[f]	Not recommended	Not recommended	Unknown (15 mg QD)[f]
<15 on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[f]	Not recommended	Not recommended	Unknown (15 mg QD)[f]

Figure 38. Evidence from randomized trials regarding therapeutic anticoagulation dose by glomerular filtration rate (GFR) (a) and in areas where RCTs are lacking (b). Dosing of non-vitamin K antagonist oral anticoagulants (NOACs) based solely on limited pharmacokinetic and pharmacodynamic data (no randomized efficiacy or safety data exist). [a]Cockcroft-Gault estimated cratinine clearance (eCrCl). [b]Apixaban dose modification from 5 mg twice per day (b.i.d) to 2.5 mg b.i.d if a person has any 2 of the following: serum creatinine (SCr) ≥1.5 mg/dl, age ≥80 years, or body weight ≤60 kg. [c]In the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF TIMI 48) study, the dose was halved if any of the following: eCrCl of 3–50 ml/min, body weight ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors). [d]This dose has no been approved for use by the United States (US) Food and Drug Administration (FDA) in this category of GFR. [e]In countries where 110 mg b.i.d. is approved, healthcare providers may prefer this dose after clinical assessment of thromboembolic vs. bleeding risk. This dose has not been approved for use by the US FDA. [f]NOAC doses listed in parenthesis are dises that do not currently have any clinical or efficacy data. The doses of NOC apixaban 5 mg b.i.d.,[b] rivaroxaban 15 mg every day, and dagigatran 75 mg b.i.d. are included in the US FDA approved labelling based on limited dose pharmacokinetic and pharmacodynamics data with no clinincal safety data. We suggest consideration of the lower dose of apixaban 2.5 mg oral b.i.d. in CKD G5 and G5D to reduce bleeding risk until clinical sfaety data are available. [g]Dabigatran 75 mg available only in the US. b.i.d., twice per day; INR, international normalized ratio. Reproduced from Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. European Heart Journal Tables 1 & 2.[61]

Practice Point 3.15.3: Duration of NOAC discontinuation before elective procedures needs to consider procedural bleeding risk, NOAC prescribed, and level of GFR (Figure 39).

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local hemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	No official indication	No official indication	**≥36 h**	**≥48 h**
CrCl <15 mL/min	No official indication for use There is no need for bridging with LMWH/UFH			

Figure 39. Advice on when to discontinue non-vitamin K oral anticoagulants (NOACs) before procedures. Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk. Low risk is defned as a low frequency of bleeding and/or minor impact of a bleed. High risk defned as a high frequency of bleeding and/or important clinincal impact. Adapted from Heidbuchel *et al*.[60]
[a]Many of these people may be on lower dose of dabigatran (110 mg twice per day [b.i.d]) or apixaban (2.5 mg b.i.d), or have to be on the lower dose of rivaroxaban (15 mg OD) or edoxaban (30 mg OD). Dabigatran 110 mg b.i.d has not been approved for use by the United States Food and Drug Administration. CrCl, creatinine clearance, LMWH, low-molecular weight heparin; UFH, unfractionated heparin. Reproduced from Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. European Heart Journal Table 3.[61]

CHAPTER 4. MEDICATION MANAGEMENT AND DRUG STEWARDSHIP IN CKD

Medication management is an important component of the care of people with CKD. Medications can be highly beneficial, but some may be toxic, are excreted by the kidney, may have narrow therapeutic windows, or may have no proven clear evidence of benefit or indication in people with CKD.

Drug stewardship refers to the effective, safe, and sustainable use of medications by all staff and physicians, encompassing the whole cycle of medication use. Medications need to be prescribed responsibly, monitored for efficacy and safety, and when they do not or no longer serve their intended purpose, discontinued. This chapter discusses key concepts in the processes of drug stewardship in people with CKD. It is beyond the scope of this guideline to list all the medications that may have altered risks/benefits in people with CKD. Such information is widely available in documents which may exist at local, regional, or national bodies (e.g., British National Formulary: www.bnf.org), and in textbooks of pharmacology. However, we describe case examples to highlight key classes of commonly prescribed medications in people with CKD. This guidance is based upon knowledge of pharmacology that has universal relevance. In many cases, knowledge of altered risk/benefits of medications comes, however, from observational studies and case reports from routine care.

4.1. Medication choices and monitoring for safety

Abnormal kidney function results in alteration in pharmacokinetics and pharmacodynamics and for people with CKD, as the CKD stage worsens, so does the prevalence of polypharmacy and comorbidities.[603] People with CKD are at increased risk of inappropriate prescribing (noted to be up to 37% in ambulatory outpatient studies, and up to 43% in long-term care studies[604, 605]) Thus, improved understanding and collaboration with pharmacists in developing care plans and medication review is strongly recommended.

People with CKD have reduced ability to excrete medications and/or their metabolites (which may increase adverse event risk or exaggerate/diminish efficacy) and increased sensitivity to medications (e.g., those bound to albumin in hypoalbuminemic states such as nephrotic syndrome). Additional issues include nephrotoxicity, diminished tolerance of side effects in the context of coexisting comorbidities or older age, and lack of adequate evidence for either benefit or harm of specific compounds, due to historical exclusion of people with (advanced) CKD from most clinical trials.[603, 606]

As in all medical decision-making, healthcare providers should consider the indication, risk-benefit profile, and potential nephrotoxicity while balancing accessibility, availability, local health policies, cultural practices, affordability, and patient preferences.

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, consider the benefits versus potential harms.

Between 18%–20% of people with CKD G3–G5 receive at least one potentially inappropriate nephrotoxic medication annually, primarily NSAIDS, nephrotoxic antivirals, and bisphosphonates.[607] Nephrotoxic medications may be indicated in people with CKD if expected benefits exceed potential harms.[608] Whenever possible, healthcare providers should strive to use non-nephrotoxic alternatives. Common nephrotoxic medications to be aware of and potential alternatives that could be prescribed instead are listed in Table 32. While some potentially nephrotoxic medications have viable alternatives, the alternatives may be less potent or there is limited comparison data on clinical outcomes, safety, and cost-effectiveness.

Nephrotoxic medication	Potential non-nephrotoxic alternatives
Analgesics	
NSAIDs: Nephrotoxic effects include decrease in GFR through reduction in prostaglandin dependent kidney blood flow, allergic interstitial nephritis (AIN), and nephrotic syndrome[603]	Acetaminophen
Antimicrobials	
Aminoglycosides: accumulates in the proximal tubular cells and disrupts phospholipid metabolism, resulting in cell apoptosis and acute tubular necrosis (ATN)[609, 610]	Cephalosporins Carbapenems
Vancomycin: unclear cause of nephrotoxicity, but likely related to ATN and possible AIN[609, 610]	Linezolid Daptomycin[610]
Sulfamethoxazole-trimethoprim: AIN, ATN, crystalluria within the distal convoluted tubule and reversible inhibition of the tubular creatinine secretion[610]	Clindamycin + Primaquine Pentamidine Atovaquone
Gastrointestinal medications	
Proton pump inhibitors: may result in AKI and CKD due to tubulointerstitial nephritis and AIN[611, 612]	H2-receptor antagonists
Cardiovascular medications	
Warfarin: glomerular hemorrhage, oxidative stress causing kidney tubular damage, and direct effects on kidney vascular calcification by vitamin K–dependent alterations of matrix Gla protein[613, 614]	Non-vitamin K antagonist oral anticoagulants (NOAC)
Other	
Lithium: NDI as well as CKD from chronic tubulointerstitial nephropathy[615]	Aripiprazole Lamotrigine Quetiapine Valproate

Table 32. Key examples of common medications with documented nephrotoxicity and, where available, selected non-nephrotoxic alternatives. CKD, chronic kidney disease; GFR, glomerular filtration rate; i.v., intravenous; NSAID, nonsteroidal anti-inflammatory drugs. From Hall RK et al. Nature Rev Nephrol (submitted).[616]

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.

Ensuring a safe use of medication requires careful monitoring for adverse effects and efficacy. A key example includes the need to monitor potassium and creatinine during the initial weeks of treatment with ACEi and ARBs (Figure 16).[19] Medications such as gentamicin and vancomycin have a narrow therapeutic range, with higher trough levels commonly associated with AKI, and so require close monitoring of GFR and medication levels during prolonged treatment.[610] Other medications, such as lithium or methotrexate require at least annual monitoring of creatinine to evaluate potential risks of nephrotoxicity.

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

Kidney disease can be induced or accelerated by the use of certain over-the-counter (OTC) medications, herbal remedies, and other dietary supplements. One of the most used class of OTC analgesic medications is NSAIDS. NSAIDs are associated with interstitial nephritis, analgesic nephropathy, and hypertension.[617] Indiscriminate chronic OTC NSAID use has been associated with a higher risks of kidney failure compared to non-use[618-621] and should be discouraged.[619-622] However, judicious NSAID use, under careful supervision of a nephrologist, may be preferred to other pain medications such as opioids that have stronger associations with adverse events.[623, 624] Proton pump inhibitors are also common OTC medications in some countries that have been associated with AKI and CKD due to tubulointerstitial nephritis and acute interstitial nephritis.[611, 612]

The use of herbal compounds remain highly prevalent in some countries and cultures.[625] These products are often used in an unmonitored setting without the input of healthcare providers. Many of these remedies are composed of natural compounds with complex active ingredients that have not been evaluated in people with CKD and/or that may lead to many different adverse effects. The frequency of CKD associated with herbal remedy use is not known and is likely different in different parts of the world, depending on local availability and reasons for use. Examples include aristolochic acid nephropathy or nephrotoxicity due to alkaloid compounds often found in Chinese herbal remedies.[626] However, cases of nephrotoxicity have been reported for many other herbal remedies globally.[625, 627, 628] The potential toxicity of herbal remedies may be enhanced by coexisting volume depletion and by other illness or medication use.

Dietary supplements are likewise readily available, not classified as OTC medications, and thus not regulated. Although laws pertaining to dietary supplement labeling prohibit specific claims for the treatment or prevention of disease, these products are widely used as "alternative" or "complementary" therapy. Patients and providers often assume these products are at least safe and possibly effective. Their pharmacokinetics may be unknown

and potential toxicity unstudied. Classic examples include creatine supplements used for body building that have been associated with AIN.[629, 630] Another example is vitamin C (ascorbic acid) supplements which in excess can lead to tubular calcium oxalate crystal deposition.[631]

Healthcare providers are encouraged to routinely inquire about the use of herbal remedies and recommend stopping any unprescribed alternative remedy that may pose a threat for (kidney) health. Figure 40 below lists common herbal remedies and dietary supplements arranged by the countries where the adverse effects were reported, to increase awareness and facilitate discussions.

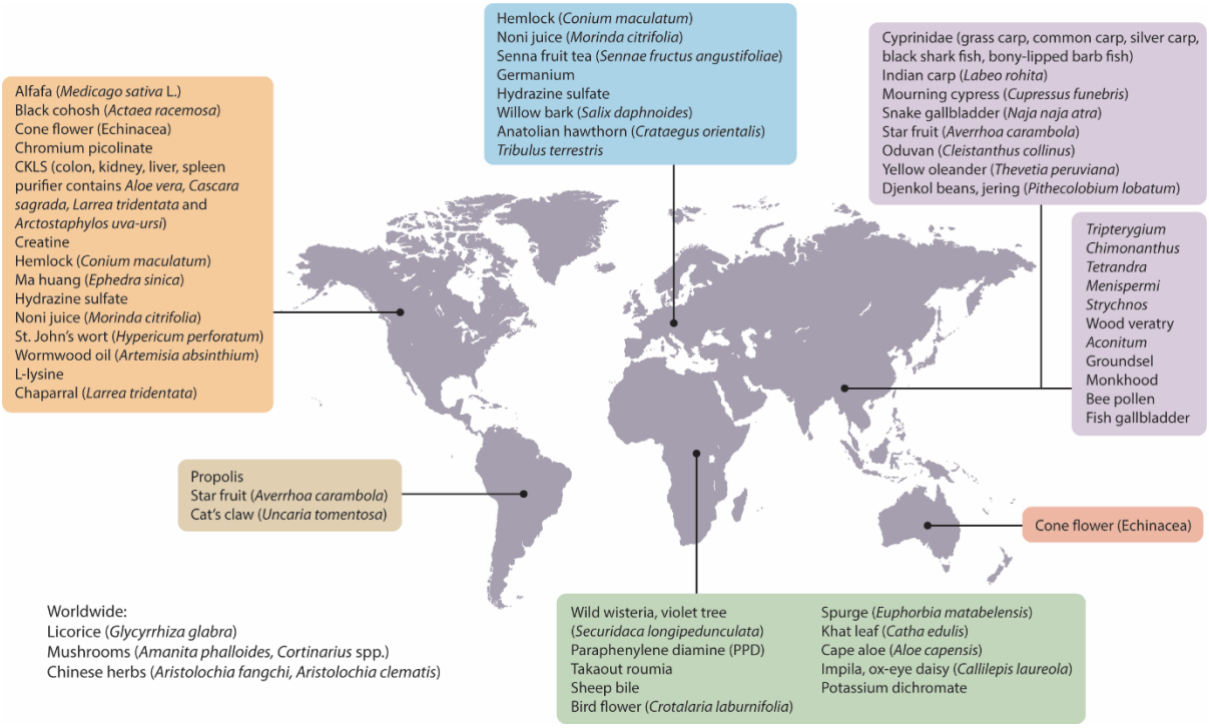


Figure 40. Selected herbal remedies and dietary supplements with evidence of potential nephrotoxicity, grouped by the continent from where the reports first came from. Yang, Bo et al.[626], Gabardi S et al.[632]; Perazella MA,[633] et al. From Hall RK et al. Nature Rev Nephrol (submitted).[616]

Special considerations

Global access to medications

Access to medications varies globally. Approximately 30% of the world population lacks timely access to quality medications. The International Society of Nephrology (ISN) report that only 35% of patients in low resources settings have access to ACEi/ARBs, statins, and insulin.[634] There are also numerous barriers to additional important medications for management of CKD complications, such as erythropoietin analogues, iron infusion, and phosphate or potassium binders.

There are growing concerns regarding the use of falsified and substandard medications in low to lower-middle income countries as they pose potential harm, particularly to those people at risk of and with CKD. Patients and their families should be

aware that medication falsification is often associated with illicit internet supply. Many vulnerable communities and people with low health literacy and those in countries with less rigorous regulatory systems are more at risk of medication falsification. Therefore, increased global awareness is important and patients should be provided with appropriate education and follow-up with relevant support in accordance with local health policies.

Medications and pregnancy

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

When pregnancy is not desired, we note that while the effect of different forms of contraception on GFR is unknown,[635] oral contraceptives are associated with increased blood pressure and hypertension.[636] Non-oral hormonal contraceptives have a less clear impact on blood pressure.[636]

Pregnancy may pose a risk of CKD progression for people with established CKD, and some recommended medications to slow or prevent CKD progression are teratogenic (such as ACEi/ARBs, or mammalian target of rapamycin [mTOR] inhibitors) or have not been studied in this population.[637] Some CKD-specific medications should be continued during pregnancies such as hydroxychloroquine, tacrolimus, cyclosporin, eculizumab, prednisone, azathioprine, colchicine, and intravenous immunoglobulin. A thorough medication chart review is necessary to replace teratogenic medications prior to conception, or whenever this is not possible, ensure a strict monitoring plan with cessation of potentially teratogenic medications at conception.[638] A similar approach should be undertaken during lactation recognizing that some medications suitable for use during pregnancy may not be appropriate for lactation, and vice versa.[639] Multidisciplinary care with obstetrics and potentially other subspecialty care is required preconception and throughout pregnancy and lactation.[352]

Sex-specific aspects of medication use in CKD

Sex differences in medication safety and efficacy in people with CKD are understudied,[640-642] For example, sex differences in body weight and composition as well as physiological functions may impact drug metabolism and response. Because drug dosages are often universal, women are more likely to consume higher doses in relation to their body weight,[643-645] and this could be associated with more adverse events.[644] In people with heart failure with reduced ejection fraction, observational studies show improved survival in women with lower doses of renin-angiotensin-aldosterone system (RAAS)-blocking medications, while men benefit from higher doses.[646, 647] This may be related to lower RAAS activity in women compared to men.[648]

4.2. Dose adjustments by level of eGFR

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

Many medications and/or their active metabolites are excreted by the kidneys. Failure to properly account for the effect of GFR when designing appropriate drug-dosing regimens can predispose a person to treatment failure or adverse events.[603, 606] Although guidelines for adjustment of the dosing regimen at varying severities of CKD provided by the manufacturer are widely available in pharmacopeias, textbooks, online references, or local procedures, there may be significant differences in information provided by these resources.[649]

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 accuracy is required for dosing (e.g., due to narrow therapeutic or toxic range) and/or estimates may be unreliable, use equations that combine both creatinine and cystatin C or measured GFR may be indicated.

An assessment of GFR is important for guiding decisions related to the choice and dosing of medications. Section 1.2 addresses the accuracy of validated eGFR equations, as well as indications for use of eGFRcr-cys or mGFR.

There is inconsistency between this guidance and those found in the package inserts or classic source references for drug dosing. Regulatory agencies have not universally required pharmacokinetics in abnormal kidney function for medication approval.[650] In addition, while Cockcroft Gault formula for estimating CrCl has been used in many past pharmacokinetic studies that serve as the basis for the drug dosing, there are multiple concerns with that equation: It was developed in an era when the need for standardization of creatinine measurements was not appreciated, women and blacks were not included, and there are concerns about use of weight, which can be impacted by edema or obesity.[651] However, to date, few studies have been conducted to compare different equations for eGFR in the context of drug dosing/kinetics, etc.

There is now a recognition by major regulatory agencies that "any contemporary, widely accepted, and clinically applicable estimating GFR equation is considered reasonable to assess GFR in pharmacokinetic studies".[651, 652]

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

For assessment of CKD, it is relevant to compare the GFR according to a standard body size. For this reason, GFR estimating equations have been developed in units of ml/min per 1.73 m^2. Use of non-indexed eGFR values (ml/min) should be considered for drug dosing decisions. Given the wide dosing categories, differences in prescribed dose using ml/min per 1.73 m^2 or ml/min will only be for very large or very small individuals.[653]

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

In patients with rapidly changing health status, it can be a challenge to estimate the GFR. Serum concentrations of filtration markers may be changing because of changes in true GFR and/or in nonGFR determinants of the marker (Section 1.2). In such settings for people who require medications that are impacted by or could impact GFR, healthcare providers should regularly assess risk, benefits, and value of the medication, consider higher or lower doses than indicated. Where possible, use medication level testing to guide dosing.[608, 654]

Special considerations

Dose adjustments in cancer

GFR plays a large role in determining anticancer therapy, including anticancer agent selection, dosing, and eligibility for investigational drugs and clinical trials.[655, 656] In most cases, general practice guideline-recommended methods for GFR evaluation may also be adopted in oncology practice and clinical trials.[644, 645] BSA-adjusted eGFR may be indicated for selected specific situations like carboplatin dosing, and directly mGFR as the preferred method to guide the initial dosing for a select group of anticancer drugs including, but not limited to, carboplatin, cisplatin, and methotrexate, or in cancer patients in whom eGFR may be inaccurate (Section 1.2).

Dose adjustment in children/neonates

In addition to the usual weight-based dosing for children, specific guidance on drug dosing should be followed for neonates who have lower GFR than those outside the neonatal period.

Dose adjustment in pregnancy

Creatinine decreases physiologically during pregnancy due to glomerular hyperfiltration, and BSA varies. This creates challenges for using GFR or eGFR equations.[352] In such settings for people who require medications that are impacted by or could impact GFR, healthcare providers should regularly assess risk, benefit, and value of medications.

4.3. Polypharmacy and drug stewardship

People with CKD are particularly susceptible to polypharmacy due to multiplicity of comorbidities and multiple physicians or health system encounters related to those. Most people with CKD not treated with dialysis receive 6–12 different medications per day.[643] Polypharmacy leads to increased pill burden, and potential harm due to medication errors and drug-drug interactions. Thus, health care providers should be diligent in assessing medication types, number, doses, and potential interactions. Drug stewardship promotes safe medication use throughout the course of therapy. Medications need to be prescribed responsibly, monitored for efficacy and safety, and when no longer required, discontinued.

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.

Medication review is essential for minimizing the occurrence of medication-related problems (e.g., in appropriately high doses, and drug interactions) that commonly occur in the CKD population.[657] If a person no longer has an indication for a medication that may contribute to kidney injury (e.g., proton pump inhibitors [PPIs]), healthcare providers should recognize the opportunity to discontinue the medication. Medication review at each clinical encounter, is an opportunity to review medication types, interval, and doses especially if the individual has experienced a decline in GFR (e.g., metformin) or physiologic changes that can impact medication volume of distribution (e.g., volume overload, sarcopenia).[658] Figure 41 discusses key steps in the medication review process. Three studies have evaluated medication review by clinical practices in people with CKD, observing reductions in the use of inappropriate medications and medication related problems, both in outpatient and inpatient settings.[646, 647] The most frequent reviews involved altering dosage or dose interval and discontinuing NSAIDs.

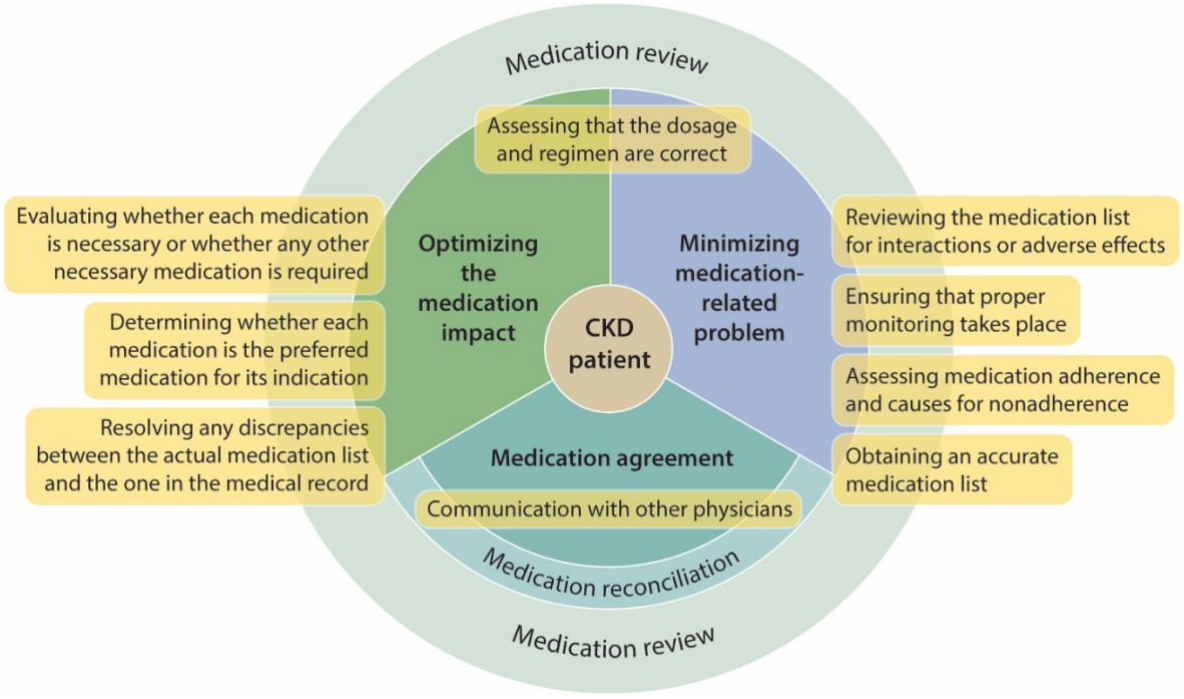


Figure 41. Suggested steps in the process of medication review and reconciliation. Best practices for medication review and reconciliation in patients with chronic kidney disease (CKD) include 8 steps[606] and can be summarized as follows: (1) Obtain an accurate medication list from the patient; (2) Evaluate whether all medications are medically necessary or whether any other medications is required; (3) Assess whether current therapy represents the "drug of choice" for each indication, individualized for each patient; (4) Evaluate the medication dosage and regimen, taking into consideration related factors such as liver dysfunction, patient size or weight (e.g., amputation, muscle wasting, over- or underweight); (5) Review the medication list for drug interactions, including drug-drug, drug-disease, drug-laboratory, and drug-food interactions; (6) Ensure that proper monitoring takes place; (7) Determine whether there are any barriers to patient adherence, and evaluate relevant laboratory values; (8) Identify and resolve any discrepancies between the medications list and the one in the medical record; Communication of performed changes in the medication chart with other physicians is necessary given the role of multiple prescribers involved in the care of patients with CKD.[607] From Hall RK et al. Nature Rev Nephrol (submitted).[616]

In the context of good drug stewardship, healthcare providers should be aware of the issue of "prescribing cascade". A prescribing cascade is a sequence of events that begins when an adverse event is misinterpreted as a new medical condition and a subsequent drug is prescribed to treat this adverse event.[659] Prior to prescribing new medications to address newly reported symptoms, it is important to first assess if the symptoms represent a side effect from an existing medication. An example of a prescribing cascade is as follows: peripheral edema because of calcium channel blocker may be managed by initiation of a new medication (i.e., diuretic) which can lead to additional adverse reactions (e.g., hypokalemia, dizziness).

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.

Sick day rules have been endorsed widely as useful guidance to people with CKD in the setting of acute, dehydrating illness. Specifically, patients receive guidance to temporarily stop the following medications: sulfonylureas, ACEi, diuretics/direct renin inhibitors, metformin, ARBs, NSAIDs, and SGLT2i (often described with the acronym SADMANS).[660] However, there is a paucity of evidence to support sick day rules to prevent AKI or other clinically relevant outcomes.[661, 662] Data suggest potential harm if people make mistakes in recognizing dehydrating illness or about which drugs to stop.[663] Figure 42 shows the steps that must occur correctly for sick day rules to be implemented appropriately. The most reported problem is failure to re-start the medication.[664] The plan to restart medications should be detailed in the medical records and clearly communicated to the patients. Patients may additionally benefit from medication review within a month to ensure appropriate medications are restarted.

Figure 42. Essential steps for appropriate sick day rule implementation. From Hall RK et al. Nature Rev Nephrol (submitted).[616]

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).

The rationale for temporary discontinuation of certain medications prior to elective surgery or procedures is to prevent perioperative AKI and other complications such as hypotension or metabolic acidosis or hyperkalemia during the perioperative period.[613] Medications that should be discontinued prior to elective surgery due to potential perioperative adverse effects are shown in Table 33.[613, 614]

Medications	Potential perioperative adverse events
ACEi/ARB	Hypotension, AKI
Diuretics	Volume depletion, AKI
SGLT2i	Ketoacidosis (starvation or diabetes)
Aminoglycosides	Acute tubular necrosis/AKI
NSAIDs	AKI, acute interstitial nephritis (AIN)

Table 33. Medications that should be temporarily discontinued before elective surgeries and potential perioperative adverse events associated with their use. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drugs; SGLT2i, sodium glucose cotransporter-2 inhibitor

There is consistent evidence that withholding RASi is associated with lower risk of perioperative hypotension in various types of surgery and procedures (noncardiac surgery, cardiac surgery, and coronary angiography).[615, 665, 666] The evidence that withholding RASi would lower perioperative AKI is less consistent as affected by fewer studies with low sample sizes.[667, 668] In the surgical context, antihyperglycemic agents such as sulfonylureas, metformin and SGLT2i would be held because of fasting prior to the surgery. Case reports, case series and a systematic review of 47 cases[617, 622, 669] support the current recommendations that SGLT2i should be withheld at least 3–4 days prior to the elective surgery.[619, 620]

Temporal discontinuation of medications to manage adverse events is indicated in most cases. However, fear for adverse event recurrence often results in failure to resume treatments. In CKD, hyperkalemia or AKI are not uncommon adverse effects of RASi treatment, to which clinical guidelines recommend discontinuation of RASi and therapy reinitiation at low dosages when the event is resolved.[19, 303, 670, 671] Despite this advice, permanent discontinuation of RASi seems to be the most common clinical reaction to occurrence of adverse events.[470, 672] Observational studies consistently show that withholding RASi medication compared to continuing treatment after these adverse events is associated with a lower recurrence of adverse events, but conversely a higher risk of MACE and death, for which RASi is mainly indicated.[398-402] See Section 3.10 on hyperkalemia management.

In all these situations, enhanced communication with the patients, and between inpatient and outpatient teams is necessary to ensure resumption of medications in a timely manner.

Special considerations

Many children with CKD with underlying tubular disorders have an obligate urine output irrespective of their hydration status and are at particularly high risk of hypotension and AKI during an acute dehydrating illness. Therefore, temporary discontinuation of medications such as diuretics and RASi that may lead to serious complications of volume depletion, such as hypotension and AKI, should be considered during illnesses. If medications are discontinued during an illness, a clear plan of when to restart the discontinued medications should be communicated to people with CKD and documented in the medical record.

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.

People with kidney disease have a role in drug stewardship and given that they may receive medications from non-nephrology healthcare providers, people with CKD should be encouraged to inform those prescribers that they have kidney disease to facilitate consideration of doses and potential side effect of medications. Thus, education and information for people with CKD inclusive for their population (i.e., literacy level, languages) is encouraged. While brochures and conversations may be useful, interactive electronic health applications have been shown to be acceptable to patients and may lead them to apply the knowledge gained more effectively.[673-677] Practical implementation tips involve printing out the results of the most recent eGFR estimation for the patient to bring along in future healthcare consultations, and/or write down a list of ongoing medications to alert other healthcare providers of medication risks and benefits.

Practice Point 4.3.1.2: Establish collaborative relationships with 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.

Strategies to improve drug stewardship by multidisciplinary interactions between nephrologists and clinical pharmacists provide safe and cost-effective care in people with CKD.[678-680] Clinical decision support systems can optimize this process through automation and decision-support integrated into the electronic medical records can support drug stewardship through alerts to healthcare providers on the need for dose adjustment to prevent adverse effects. In RCTs enrolling people with CKD, electronic clinical decision support systems have demonstrated efficacy in reducing medication errors, avoiding drug-drug interactions, and improving dose-adjustment of medications excreted by the kidneys.[681-686] Recognizing that many of these tools may not be available in all communities, the concepts of regular review and evaluation of medications by a knowledgeable healthcare provider is a critical component of care for people with CKD

Special considerations

Pediatric considerations

Parents and carers should be central to drug stewardship for children with CKD, with increasing involvement from the young person as they move towards transition.

4.4. 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.

The use of iodinated radiocontrast media has been associated with the occurrence of AKI, with varying rates reported in observational studies depending on the population studied, the type, route and dose of agent being used, and the definition of nephrotoxicity. The term "contrast-induced AKI" has been traditionally coined to describe this condition;[687] but subsequent research characterizing this entity suggests causal links to be weak,[687-689] and the term "contrast-associated AKI" has been suggested instead.

While there is potential risk for AKI with contrast administration in people with CKD G4–G5, caution should be exercised in withholding contrast treatment or evaluation of a potentially fatal condition solely based on GFR.[690, 691] When eGFR is ≤30 ml/min per 1.73 m^2, the risks and uncertainties of delayed or suboptimal imaging should be balanced against the risks of contrast-associated AKI. Table 34 describes potential causes of contrast-associated AKI identified in available studies that may suggest an approach to people with CKD (Figure 43).

Patient associated	Procedure associated
Reduced GFR, acute or chronic[a]	High-osmolar contrast
Diabetes mellitus[b]	Large volume of contrast
Reduced intravascular volume	Serial contrast procedures
Concomitant nephrotoxic medications	Intra-arterial procedures

Table 34. Potential risk factors for contrast-associated acute kidney injury (AKI). GFR, glomerular filtration rate. [a] Defined as estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2 with other risk factors or eGFR <30 ml/min per 1.73 m^2. [b] Augments risk in patients with underlying kidney function impairment. From: Cashion W. *et al*. Radiographic Contrast Media and the Kidney. CJASN; 2022. 17: 1234-1242[692]

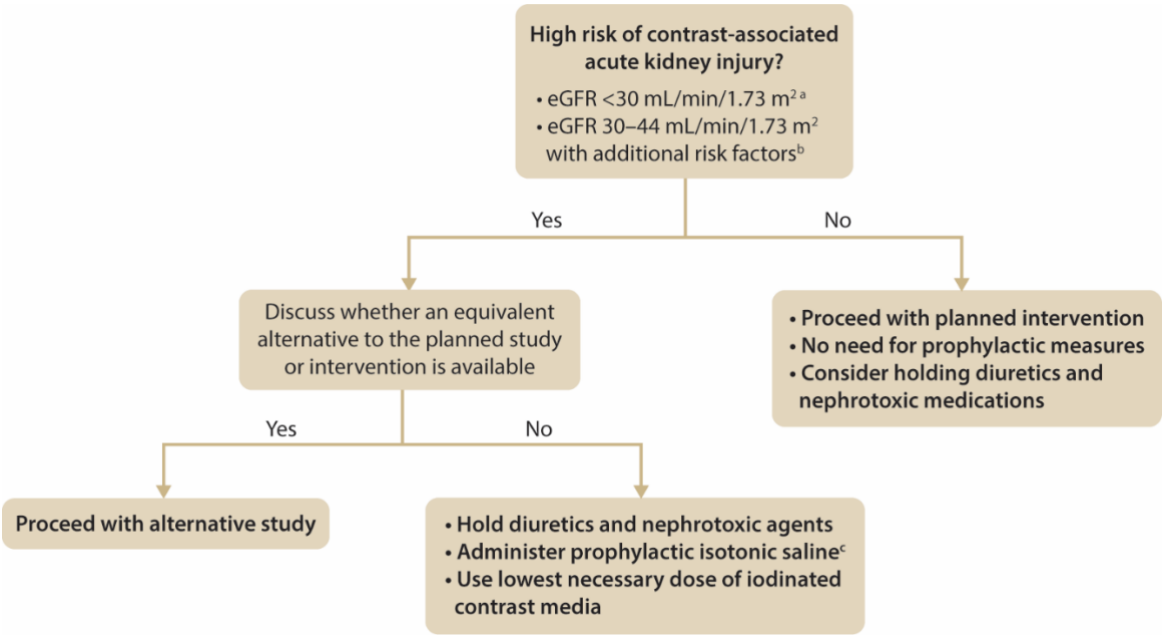


Figure 43. Suggested algorithm to people with chronic kidney disease (CKD) requiring iodinated contrast media.[691] eGFR, estimated glomerular filtration rate. [a]This includes people receiving hemodialysis and peritoneal dialysis with residual GFR. [b]Risk factors include age, diabetes, hypertension, volume depletion, and concomitant nephrotoxins. [c]Hydration is not indicated in cases of hypervolemia or decompensated heart failure.

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.

The reported risk of contrast-associated AKI is higher with procedures involving arterial administration compared with venous administration of contrast.[693] This difference in risk may be due to differences in patient populations (those who require arterial contrast are likely to have comorbidities that increase the likelihood of AKI) or to differences in the nephrotoxicity of intra-arterial contrast material.

Known risk factors for contrast-associated AKI are the volume of contrast material, proteinuria, hyperglycemia, and use of RASi. The highest risk for AKI is associated with interventional (rather than diagnostic) coronary angiography (particularly in the setting of acute myocardial infarction). This may relate to the higher volume of contrast used in interventional procedures and hemodynamic instability associated with acute myocardial infarction situation.[694, 695]

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

The Work Group agrees with the consensus statements from the American College of Radiology and the National Kidney Foundation,[690] which include:

- Use of low-osmolality contrast media (LOCM) and iso-osmolarity contrast media (IOCM)
- Use of minimum radiocontrast dose to achieve a diagnostic study.
- Withdrawal of nonessential potentially nephrotoxic medications (e.g., NSAIDs, diuretics, aminoglycosides, amphotericin, platins, zoledronate, methotrexate) in people with AKI or eGFR <30 ml/min per 1.73 m^2 for 24–48 hours before and 48 hours after radiocontrast exposure
- In people with eGFR >30 ml/min per 1.73 m^2 and without evidence of AKI, metformin need not be stopped prior to iodinated contrast media (ICM) administration and there is no need for testing to evaluate GFR afterward. For people with AKI or an eGFR ≤30 ml/min per 1.73 m^2, it remains appropriate to stop metformin at the time of or prior to ICM injection and should not be restarted for at least 48 hours and only then if GFR remains stable and the ongoing use of metformin has been reassessed by the clinical team.[696]
- Given the lack of strong evidence demonstrating that continuing RAASi is beneficial, referring healthcare providers should consider withholding RAASi in people at risk for ≥48 hours before elective contrast-enhanced computed tomography (CT) to avoid the potential for hypotension and hyperkalemia should contrast-associated acute kidney injury (CA-AKI) develop. RAASi may be restarted if CA-AKI does not occur or following the return of GFR to baseline.
- Consideration of avoiding dehydration for people not undergoing dialysis and who have eGFR <30 ml/min per 1.73 m^2 or AKI. Intravenous sodium-based isotonic crystalloid with either bicarbonate or chloride as the component anion can be considered the standard of care to mitigate CA-AKI risk.[692] However, sodium chloride is generally preferred given its lower cost, availability, and avoidance of the risk for errors in formulation. Oral hydration can also be an option for outpatients. There are no established dosing or timing recommendations for how oral hydration should be administered. Some encourage patient-directed oral hydration before and after the scan (e.g., up to 2 liters).[692, 697]
- Use of N-acetylcysteine, ascorbic acid, furosemide, dopamine, fenoldopam or calcium channel blockers as preventative measures of CA-AKI has not been shown to be a consistent benefit.[692]
- Prophylactic pericontrast hemodialysis has been shown to be potentially harmful and is not recommended.[692]

Special considerations

Global access to contrast agents

There are cost implications in lower income countries and lower-middle income countries as iso-osmolar contrast media are more expensive.

4.4.2. Gadolinium-containing contrast media

Gadolinium chelates used during magnetic resonance imaging (MRI) has previously been reported to cause nephrogenic systemic fibrosis (NSF) before 2010 and the mechanisms have been articulated.[698] Note that incidence of this condition has not been reported later than 2012, thus raising the question as to the true risk of this condition.[699]

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.

People who are at greatest risk for NSF include those with AKI, undergoing KRT, and those with CKD G4–G5. Most unconfounded cases have been associated with American Colleague of Radiology group I gadolinium-based contrast media (e.g., gadodiamide, gadopentate dimeglumine, gadoversetamide) and there is additional risk with repeated doses.[700, 701]

Hence, in people with GFR<30 ml/min per 1.73 m^2, the use of newer linear and macrocyclic gadolinium-based contrast media such as gadobenate dimeglumine, gadobutrol, gadoteridol, gadoterate meglumine and gadoxetate disodium should be preferred.[702, 703]

Special considerations

Global access to gadolinium-contrast agents

There are cost implications in lower income countries and lower-middle income countries as the non-linear chelated preparations are more expensive.

Pediatric considerations

Considerations specific to the use of gadolinium preparations in young children and neonates must also be contemplated in addition to the general admonishments against their use in situations of GFR <30 ml/min per 1.73 m^2. In particular, the FDA currently does not license any gadolinium-based contrast media product for use in children <2 years of age and, likewise, the European Medicines Agency (EMA) cautions against the use of any gadolinium-based contrast agents (GBCA) in a child <1 year of age.

In recognition of the inability to accurately measure GFR in the neonate and, by extension, the clearance of compounds such as gadolinium, all nephrologists and radiologists must exercise caution in terms of use of gadolinium-based contrast media in this potentially high-risk population, and all other imaging modalities should be considered prior to choosing one requiring gadolinium exposure. Though not based on specific evidence, some have

suggested the avoidance of high-risk gadolinium agents in very young children (e.g., neonates younger than 4 weeks of age).[704]

Moreover because of kidney immaturity in fetuses, neonates, and infants, this population (and consequently pregnant women because of the risk to the fetus) is considered potentially at risk for NSF.[705] However, the number of reported cases of NSF in the pediatric population is lower than in the adult population.[706] There is no convincing evidence that pediatric patients have an increased risk compared with adults.

CHAPTER 5. OPTIMAL MODELS OF CARE

5.1. Referral to specialist kidney care services

Early identification and referral to specialist kidney care services for people with CKD has the potential to reverse, delay, or prevent progression of disease and is a key focus of international initiatives in the context of the global "epidemic" of kidney disease. The goals of early identification and referral to specialist kidney care services are several-fold and include:

- Ensuring a specific diagnosis for CKD is sought, where appropriate,
- Provision of specific therapy based on diagnosis,
- Slowing/arresting CKD progression,
- Evaluation and management of comorbid conditions,
- Prevention and management of CVD
- Identification, prevention, and management of CKD-specific complications (e.g., malnutrition, anemia, bone disease, acidosis),
- Planning and preparation for KRT (e.g., choice of modality, access-placement and care, preemptive transplantation),
- Psychosocial support,
- Provision of conservative care and palliative care options where required.

Practice Point 5.1.1: Refer adults with CKD to specialist kidney care services in the following circumstances (Figure 44):

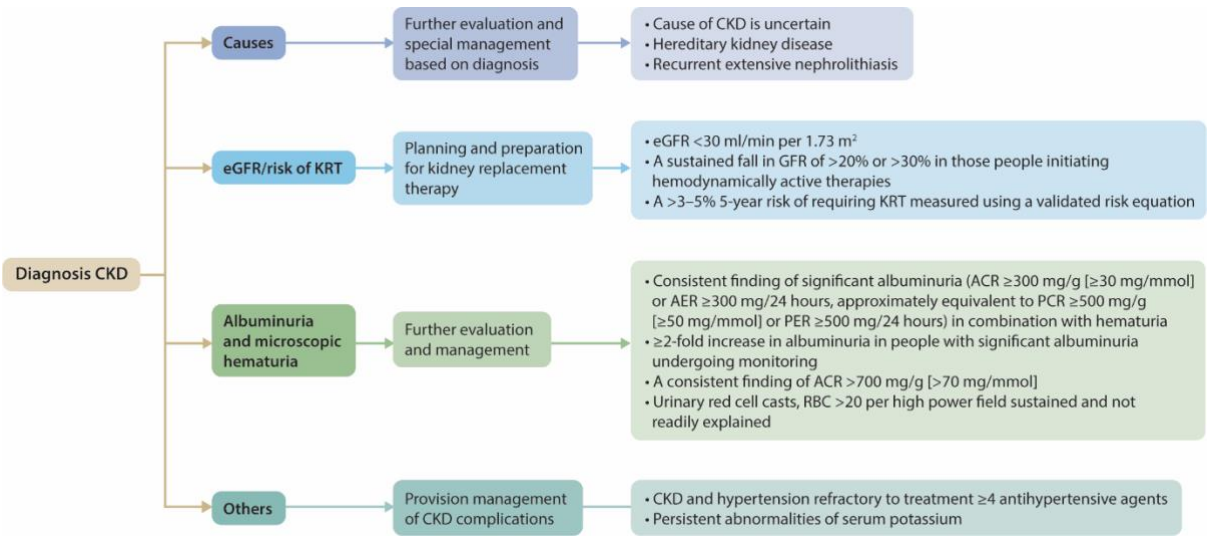


Figure 44. Circumstance for referral to specialist kidney care services and goals of the referral.
ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; PCR, protein-creatinine ratio; RBC, red blood cells

The scope of nephrology practice includes a wide variety of conditions, not only kidney failure but also acute and chronic primary and systemic diseases involving individual elements of the kidney, resistant hypertension, and biochemical derangements. Thus, there are many potential benefits of nephrology referral in addition to those more commonly recognized such as identification of reversible causes of CKD, provision of treatment to slow progression of CKD, management of the metabolic complications of CKD G4–G5, and preparation for dialysis and transplantation.

Central to achieving the best outcomes for people with CKD regardless of the reason for referral is the timeliness of referral. Application of risk prediction tools (Chapter 2) may aid decision-making in terms of identifying those at risk of progression and determining action thresholds for multidisciplinary care and placement of access for KRT, or referral to transplantation. Current recommendations to use validated risk equations to ascertain those at high probability of kidney failure within 2 years should prompt actions that align with provision of appropriate education activities, review of understanding, and decision-making and prompting referrals to other healthcare providers (e.g., vascular access surgeons, transplant teams, etc.).

Risk-based guided referral was compared with guideline referral criteria in a cross-sectional study from UK.[707] Analysis revealed that approximately 40% of patients classified as high risk of progression to kidney failure by KFRE (>3% by 5 years) were missed by guideline referral criteria. Moreover, a model predicting the timing of clinical outcomes, validated in a multicenter prospective cohort study of 1517 patients aged ≥65 years old with eGFR 10–30 ml/min per 1.73 m^2, showed good performance for predicting the timing and occurrence of KRT.[708] Using this prediction model to guide referral for vascular access preparation resulted in less unnecessary arteriovenous fistula surgeries than using eGFR thresholds.

In this section, we consider the evidence relating to timely referral for planning KRT in people with progressive CKD. The literature concerning late referral has been remarkably consistent with both clinical studies and narrative reviews identifying several adverse consequences of late referral and related benefits of early referral (Table 35).

Consequences of late referral	Benefits of early referral
Severe hypertension and fluid overload	Delay needs to initiate KRT
Low prevalence of permanent access	Reduced need for urgent dialysis using temporary access
Delayed referral for transplant	Greater choice of treatment options
Higher initial hospitalization rate	Increased informed freedom of choice of KRT modality
Higher 1-year mortality rate	Reduced hospital length of stay and costs
Less choice of KRT modality	Improved nutritional status
Worse psychosocial adjustment	Better management of CVD and comorbid conditions
	Improved survival

Table 35. Benefits and consequences of early versus late referral. CVD, cardiovascular disease; KRT, kidney replacement therapy

Both individual and healthcare system factors are associated with late referral for KRT planning. A systematic review of 18 studies and physician surveys identified specific factors responsible for late referral for KRT as shown in Table 36.[709] Therefore, we encourage each nephrology program to explore factors associated with late referral to improve referral patterns appropriately.

Patient-related factors	Healthcare system-related factors
Age	Health insurance status
Race	Type of referring physician
Comorbid illness	Type of referring center
Etiology of kidney disease	Health system and/or Physician rationing
Noncompliance	Distance to dialysis center
Socioeconomic status	

Table 36. Factors associated with late referral for kidney replacement therapy planning.

People with kidney disease have never been randomized to early or late referral to nephrology services and the definition of late referral in the published studies varied between 1 and 12 months. Three months is probably less than the absolute minimum amount of time required for assessment, education, preparation for KRT, and creation of access, but 3 months is the most frequently employed definition.

A systematic review of 40 studies showed that early referral was associated with better clinical and biochemical outcomes such as improvement in mortality at 3 and 5 years, decrease in hospitalizations, better access to vascular access and KRT with peritoneal dialysis, as well as improvements in BP, hemoglobin, and serum albumin (Table 37).[710] A retrospective study of 105,219 patients (Early referral 21,024 patients and Late referral 84,195 patients) showed that early referral to nephrology care was associated with slower progression of CKD as significantly more patients in early referral group did not change their CKD stage (65%–72.9% vs. 52%–64.6%, $P < 0.05$).[711]

Outcomes	Relative risk comparing early vs. late referral
Receive permanent vascular access	RR: 3.22; 95% CI: 2.92–3.55
Initiation of KRT with peritoneal dialysis	RR: 1.74; 95% CI: 1.64–1.84
3 month mortality	OR: 0.61; 95% CI: 0.55–0.67
5 month mortality	OR: 0.66; 95% CI: 0.60–0.71
Outcomes	**Mean difference in early vs. late referral**
Initial hospitalization, days	-9.1; 95% CI: -10.92–-7.32
Systolic blood pressure, mm Hg	-3.09; 95% CI: -5.23–-0.95
Diastolic blood pressure, mm Hg	-1.64; 95% CI: -2.77–-0.51
Hemoglobin, g/dl	2.76; 95% CI: 2.53–2.99
Serum albumin, g/dl	1.92; 95% CI: 1.83–2.01

***Table 37. Outcomes examined in* a systematic review by *Smart et al.*[710]** KRT, kidney replacement therapy; OR, odds ratio; RR, relative risk

Local practice and resources will dictate local referral practices. Regardless of the healthcare system, delay, or prevention of progression of both CKD and its complications will be of value to both individuals and healthcare systems. Local organizations will determine the best methods of communication and interaction between people with CKD, kidney care specialists, and primary care physicians.

Technology may be used to promote appropriate nephrology referral. Embedding clinical practice guidelines into clinical information systems may effectively create a reminder system for primary care physicians. Clinical decision support systems (CDSS) could also improve referral criteria adherence. The smart phone application, Nefroconsultor, which uses KDIGO referral criteria was shown to increase the rate of appropriate referral by 28.8%.[712]

Implementation of referral guidelines will inevitably lead to an increased workload for specialist kidney care services. However, introduction of local initiatives in conjunction with primary care providers can improve the appropriateness and quality of the referral. A checklist for goal-directed care in CKD should be considered. Local initiatives combined with national policy and practice changes can lead to an improvement in the outcomes for people with CKD regardless of the level of resources available.

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 [20mg/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.**

Children with known or suspected CKD or who are at risk of CKD (as outlined above) should be referred to specialist care. This allows for timely investigations and diagnosis. Early integration of children with CKD into nephrology services will ensure optimal management of pediatric complications of CKD (including growth restriction) and will promote access to pre-emptive transplantation (the KRT of choice).

5.2. Care of people with CKD G4–G5

5.2.1. Prevalence and severity of symptoms

CKD confers a high burden of uremic symptoms that may be underrecognized, underdiagnosed and undertreated.[713] As kidney disease progresses, affected people experience an increasing burden of adverse uremic symptoms. These symptoms can impair their health-related quality of life (HRQoL) by interfering with social relationships, financial instability, and contributing to overall poor well-being.[714] Patient-reported outcomes, including HRQoL and symptoms, are often identified by people with CKD as more important to them than clinical outcomes, such as survival.[715, 716] A recent systematic review of 126 patient-reported outcome studies involving people with CKD G1–G5, not on KRT, identified the most common symptoms experienced, in terms of prevalence and severity in this population (Figure 45).[717] The most prevalent symptom reported in the CKD population not on KRT was fatigue at 70% (95% CI: 60%–79%), whilst in the identified control population without CKD, fatigue prevalence was 34% (95% CI: 0%–70%). In terms of the symptoms reported as the most severe, sexual dysfunction had the highest severity score. This review also looked at populations receiving dialysis and/or transplantation, allowing for the comparison of prevalence and severity across populations. This provides insight into symptoms that may be attributable to changing or deteriorating kidney function and may provide symptom targets for tracking in the care or patients, especially those with more advanced CKD, such as CKD G5.

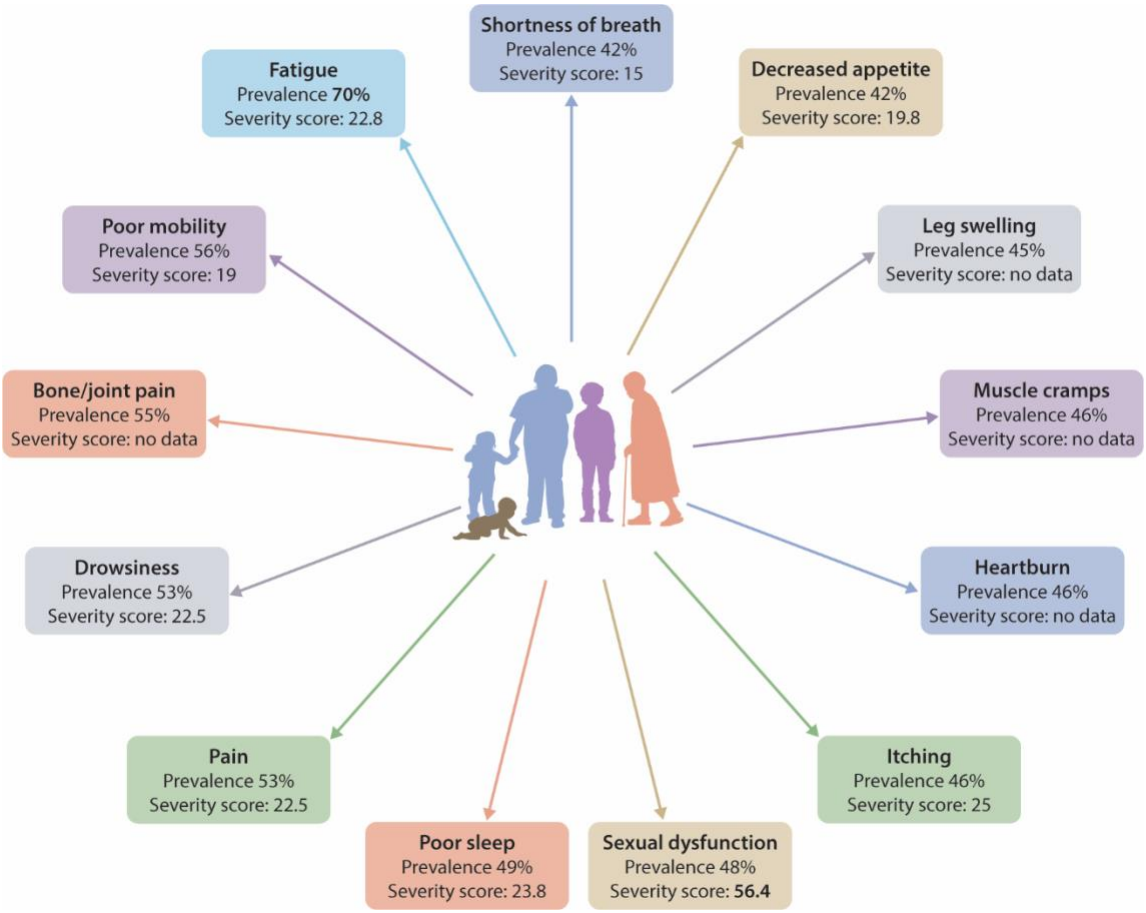


Figure 45. Common symptoms, prevalence, and severity in people with CKD. Figure developed from findings from Fletcher et al[717]. To aid comparison of symptom severity scores across different outcome measures, all mean severity scores were converted to a 0–100 scale, where a higher score indicates greater severity.

5.2.2 Identification and assessment of symptoms

Practice Point 5.2.2.1: Ask people with CKD G4–G5 about uremic symptoms at each consultation (i.e., reduced appetite, nausea, level of fatigue/lethargy) using a standardized symptomatic assessment of uremic symptoms.

The identification and assessment of symptoms in people with CKD G5 is important for highlighting changes in clinical management,[718] redirecting treatment toward patient-centered management, and may lead to discussion about appropriate supportive care options.[716] Effective two-way communication and shared decision-making should be key principles between healthcare providers and the people they treat, allowing them to work in partnership to identify symptom burden, possible treatment strategies and person-centered solutions.[713, 717, 719]

In the past, it had been challenging to find an accepted standardized approach to assess and report outcomes for those with CKD; and patient reports of their HRQoL are still rarely routinely recorded, despite increasing recognition of their importance.[719-721] In addition, many of the assessments developed have been for people on dialysis, with little validation in CKD populations not on KRT. In 2019, Verberne *et al*. described an

international standard set of outcome measures for people with CKD, developed in conjunction with people with very high-risk CKD G3–G5.[719] Within this standardized set of outcome measures there are 4 domains, with one of the domains targeting 6 patient-reported outcomes for HRQoL (fatigue, pain, general HRQoL, physical function, depression, and daily activity). To date, there is no consensus on a single preferred patient-reported outcome measure (PROM) instrument to be used to assess these symptoms. However, 3 generic tools have been recommended by the International Consortium for Health Outcomes Measurement (ICHOM) (Table 38).

PROM tool	Comments
SF-36 version 2	Widely used and well-validated in many populations. Requires a license fee.
RAND-36	Older version of the SF-36. Does not require a license fee. Only available in English and Arabic.
PROMIS and PROMIS-29	Both short forms are based on extensive item banks. Available in paper and electronic versions. Well-validated in general population with validation in people with CKD showing good reliability and sufficient validity in both adults and pediatric populations.

Table 38. Recommended patient-reported outcome measurement tools for use in people with chronic kidney disease (CKD). PROMIS, Patient-Reported Outcomes Measurement Information; SF-36, 36-item Short Form Health Survey Figure developed from Verberne et al.,[719] Selewski et al.,[722] van der Willik et al.[723]

The Patient-Reported Outcomes Measurement Information System (PROMIS) tool has been evaluated in adults and children with CKD, evidencing sufficient validity and reliability.[722-724] Further study is still needed to investigate its optimal use in routine nephrology care.

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.

The goal of effective symptom management in people with CKD is to assist them to live better with kidney disease, regardless of life expectancy, within a supportive care framework.[716] Unpleasant symptoms, such as CKD associated pruritis and emotional/psychological distress, often occur within symptom clusters and treating one symptom may potentially alleviate other symptoms.[713] Developing treatment strategies can be challenging given the complexities of managing CKD in different populations and the variation in levels of evidence for managing the different symptoms experienced, with many strategies extrapolated from studies of treatments in the general population or people on hemodialysis. For example, sexual dysfunction, is very common and one of the most severe symptoms described by people with CKD, is fraught with barriers in terms of research, from agreement of definitions, the stigma of sexual dysfunction, acknowledging the distinction between sex and gender, discordance between research priorities and patient priorities and understanding that there are variable responses to treatment in people with CKD.[725] However,

there has been some consensus that there is sufficient evidence to support guidance for some symptoms such as uremic pruritis, sleep disturbances, pain, depression, and restless leg syndrome,[716] but future research is needed to understand the determinants of symptoms such as chronic pain and evaluation of management strategies.[726] Table 39 provides an overview of the most common symptoms in CKD.

Symptom	Comment	Management strategies		
		Lifestyle and dietary	Pharmacological	Other
Pain	Management should be determined by etiology and severity	Physiotherapy, exercise and massage therapy, heat for musculoskeletal pain. Consider complementary therapies such as acupuncture.[716, 718, 727]	Use of an adapted World Health Organization (WHO) Analgesic Ladder that takes into account pharmacokinetic data of analgesics in CKD.[728] Before starting opioids, healthcare providers should assess risk of substance abuse and obtain informed consent following a discussion around goals, expectations, risks, and alternatives. Topical analgesics may be effective but used with caution to avoid adverse events due to systemic absorption. There are no studies on long-term use of any analgesics in people with CKD, therefore attention should be paid to issues of efficacy and safety.	Referral to a specialist pain clinic or palliative/supportive care clinic may be beneficial for those at risk of aberrant behaviors, adverse outcomes or in special circumstances such as end of life.[727]
Sleep disorders	Associated with fatigue, poor HRQoL,[716] May be related to pruritus, pain, anemia, anxiety/depression, shortness of breath[718]	Management of basic sleep hygiene, Exercise, Optimal positioning when sleeping, Removal of dietary or other stimulants[716]	Melatonin[729] Simple sedatives[730, 731]	Cognitive behavioral therapy,[732] Addressing contributing factors such as anemia, fluid retention, mood disorders, pain, and pruritis
Restless legs syndrome	Associated with impaired sleep and HRQoL	Management of basic sleep hygiene, Exercise, Optimal positioning when sleeping, removal of dietary or other stimulants[716]	Cessation of medications that interfere with the dopamine pathway, or trials with levodopa, non-ergot dopamine antagonists or low dose gabapentinoids[733-735]	Correction of contributing factors such as hyperphosphatemia and iron deficiency/anemia

Uremic pruritis	Associated with decreased HRQoL, and contributes to other symptoms, such as poor sleep, fatigue, and depression[716]	Acupunture[736]	Gabapentinoids with continued assessment of symptom experience and titration by a medical provider [737-739] Topical agents (capsicum, rehydrating emollients if concurrent dry skin)[739]	Ultraviolet B therapy[740] Topical cannabis can be considered [741]
Depression	May be related to CKD burden and perception, loss of control, medication effects. Associated with increased morbidity, hospitalization, and mortality and is integral to the assessment of HRQoL[716]	Exercise[742] Acupuncture [743]	Before commencing pharmacological treatment for depression, healthcare providers should be aware of the potential necessity to adjust dosage, and follow up with the patient, due to altered pharmacokinetics in CKD.[718] In some circumstances this may need to be done in conjunction with specialist psychiatric services. Options may include: • Serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) • Serotonin–norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine, mirtazapine) • Atypical antidepressants (e.g., bupropion, trazodone, nefazodone) • Tricyclic antidepressants (e.g., amitriptyline)[744-747]	Cognitive behavioral therapy[748] Social support[747] Address contributing factors (e.g.. pain, pruritis and mood disorders)
Poor appetite and anorexia	Associated with depression, malnutrition, poor HRQoL increased	Increased physical activity may increase appetite[749]	No data to support the use of appetite stimulants in people with CKD not on KRT.	Address contributing factors (pain, heartburn, mood disorders, any dental issues/mouth ulceration,

	hospitalization and mortality rates[716]		Management has not been studied systematically in CKD.[716]	constipation, social and economic factors, lack of physical activity) Dietary assessment by a dietician
Nausea and vomiting	Impact has not been assessed systematically in CKD.[716]		Pharmacological management has not been systematically studied in CKD.[716]	

Table 39. Management strategies for common symptoms in chronic kidney disease (CKD). HRQoL, health-related quality of life; G3, estimated glomerular filtration rate (eGFR) 30–59 ml/min per 1.73 m^2; G5, eGFR <15 ml/min per 1.73 m^2; KRT, kidney replacement therapy. Table adapted and updated from Davison et al 2015 Exec summary of the KDIGO Controversies Conference on Supportive Care in CKD[716]

Practice Point 5.2.3.2: Screen people with CKD G4–G5, aged >65, poor growth (pediatrics), or symptoms like 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, ideally under the supervision of accredited nutrition providers, for people with signs of malnutrition.

In different world regions, 11%–50% of adults and 20%–45% of children with CKD have malnutrition characterized by PEW.[377-379] In a European cohort of 1334 adults over the age of 65 with CKD G4–G5, 25% were found to have moderate malnutrition and the risk was increased with advancing age, female gender and psychiatric disease.[750] Malnutrition can happen at any stage of CKD and is associated with a higher morbidity and mortality, loss of muscle mass and inflammation. It can also be associated with worse outcomes with kidney transplant.[379] The risk of PEW increases as CKD progresses but is also influenced by comorbid conditions such as diabetes, autoimmune, and cardiovascular disease. PEW is thought to be driven by the damaging effect of uremic toxins on appetite and chronic inflammation.[378, 379, 750] Given the impact on prognosis and quality of life, nutritional assessment and intervention by a kidney dietitian using a validated assessment tool should be undertaken for people with CKD that present with frailty, age >65, weight loss, poor growth (pediatrics), poor appetite, and all people with CKD G4–G5 (Table 40).

Validated malnutrition assessment tool	Attributes
7-Point Subjective Global Assessment (SGA)[751]	Provides assessment points on weight change, dietary intake, digestive function, functional capacity, and metabolic stress. A nutrition focused physical exam is also performed. This updated version of the SGA is more sensitive to short term nutrition changes. A score of 1–2 indicates severe malnutrition, 3–5 is mild malnutrition, and 6–7 indicates normal nutrition status.
Malnutrition Inflammation Score[752]	Assesses malnutrition and inflammation using 10 parameters including dietary intake, anthropometric measurements, laboratory indices, as well as functional capacity. The score ranges from 0 (normal) to 30 severe malnutrition and inflammation.
Mini Nutrition Assessment[753]	Includes assessment of dietary intake, mobility, neuropsychology, and some anthropometric measurements, including weight and calf circumference. 12–14 points indicates normal nutrition status; 8–11 indicates at risk for malnutrition; 0–7 points indicates malnutrition

Table 40. List of validated assessment tools for malnutrition.

5.3. 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.

An optimal care model leads to the best outcomes for the individual, the population, and the community. The model of care varies according to CKD severity and risk of progression to kidney failure, which will determine the target population and goals (Figure 46).

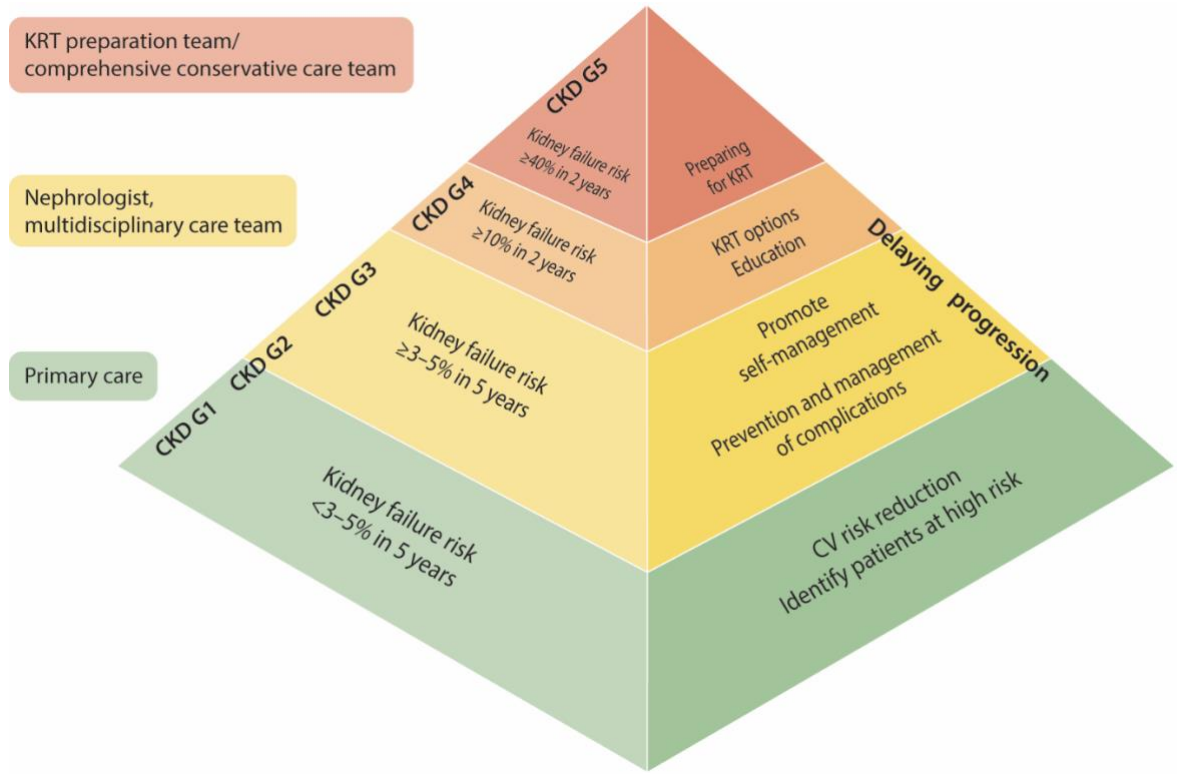


Figure 46. Optimal care model by severity of chronic kidney disease (CKD). CV, cardiovascular; KF, kidney failure; KRT, kidney replacement therapy

CKD models of care follow the same principles embodied in the chronic disease model of care (Figure 47). Each key component of the chronic care model are applied to the CKD care model.

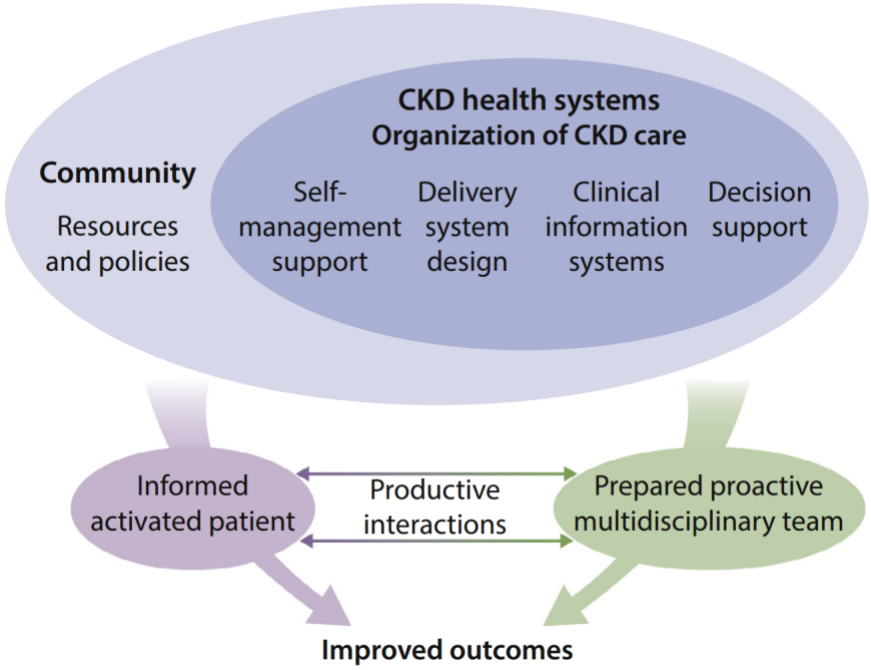


Figure 47. The chronic care model. CQM, clinical quality measure. The chronic care model emphasizes the additive benefits of different components in the system, policy, provider, and patient levels in improving clinical outcomes. CKD, chronic kidney disease. Reproduced from Improving the quality of health care for chronic conditions, Epping-Jordan JE, Pruitt SD, Bengoa R, et al., volume 13, 299–305[754]

The specific components for CKD models of care are presented in Figure 48 and include:

1. An education program which includes both general CKD and KRT education, including conservative management, where appropriate.
2. Navigation system that leads to appropriate and timely referral. This relies on a good healthcare system.
3. Surveillance protocols for laboratory and clinic visits, attention to cardiovascular comorbidities and CKD-associated comorbidities such as anemia, a vaccination program.
4. Management that includes self-management particularly lifestyle modification including diet, exercise, and smoking cessation. medications and psychosocial support for issues such as social bereavement, depression, and anxiety.
5. 3-way communication between people with CKD, their multidisciplinary specialist care team, and their primary care providers

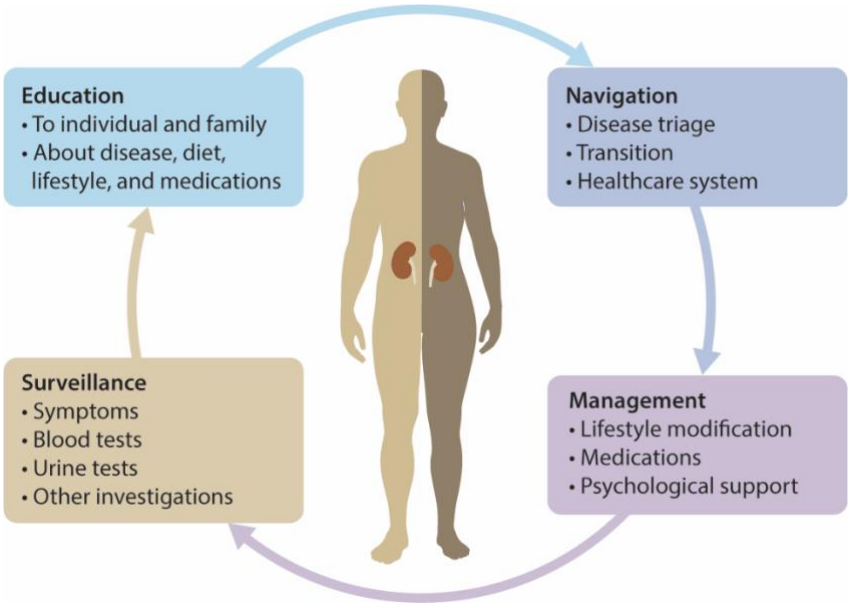


Figure 48. Specific components of the chronic kidney disease (CKD) model of care.

There are various CKD care models around the world. The key features of existing CKD care models described in systematic reviews are shown in Table 41.

Multidisciplinary care team composition	
• Nephrologist • Endocrinologist, transplant surgeon, psychologist, etc. • Nurse	• Pharmacist • Accredited nutrition provider • Social worker
Interventions	
• BP management • Diabetic management • Cardiovascular management • Anemia management • Mineral and bone disorder management • Conservative kidney management	• Education on dialysis modality selection • Vascular access planning • Transplantation evaluation • Nutritional and dietary counseling • Medication reconciliation • Vaccination program
Outcomes	
• Delay progression of CKD • Improve BP control	• Improve rate of ACEi/ARB prescription • Improve patient education

Table 41. Key features of existing chronic kidney disease (CKD) care models. ACEi, angiotensin-converting enzyme inhibitor; AR, angiotensin II receptor blocker; BP, blood pressure

Health information technology especially the internet and mobile technologies are growing rapidly. These technologies were applied to deliver CKD care in different aspects particularly during the COVID-19 pandemic.

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

An effective patient education program is a critical success factor of self-management support strategies. Education should address 3 main issues:

1. Standardized educational topics and resources,
2. Strategy to provide education effectively, and
3. Patient-centered concept.

The suggested components of effective patient education programs are illustrated in Figure 49.

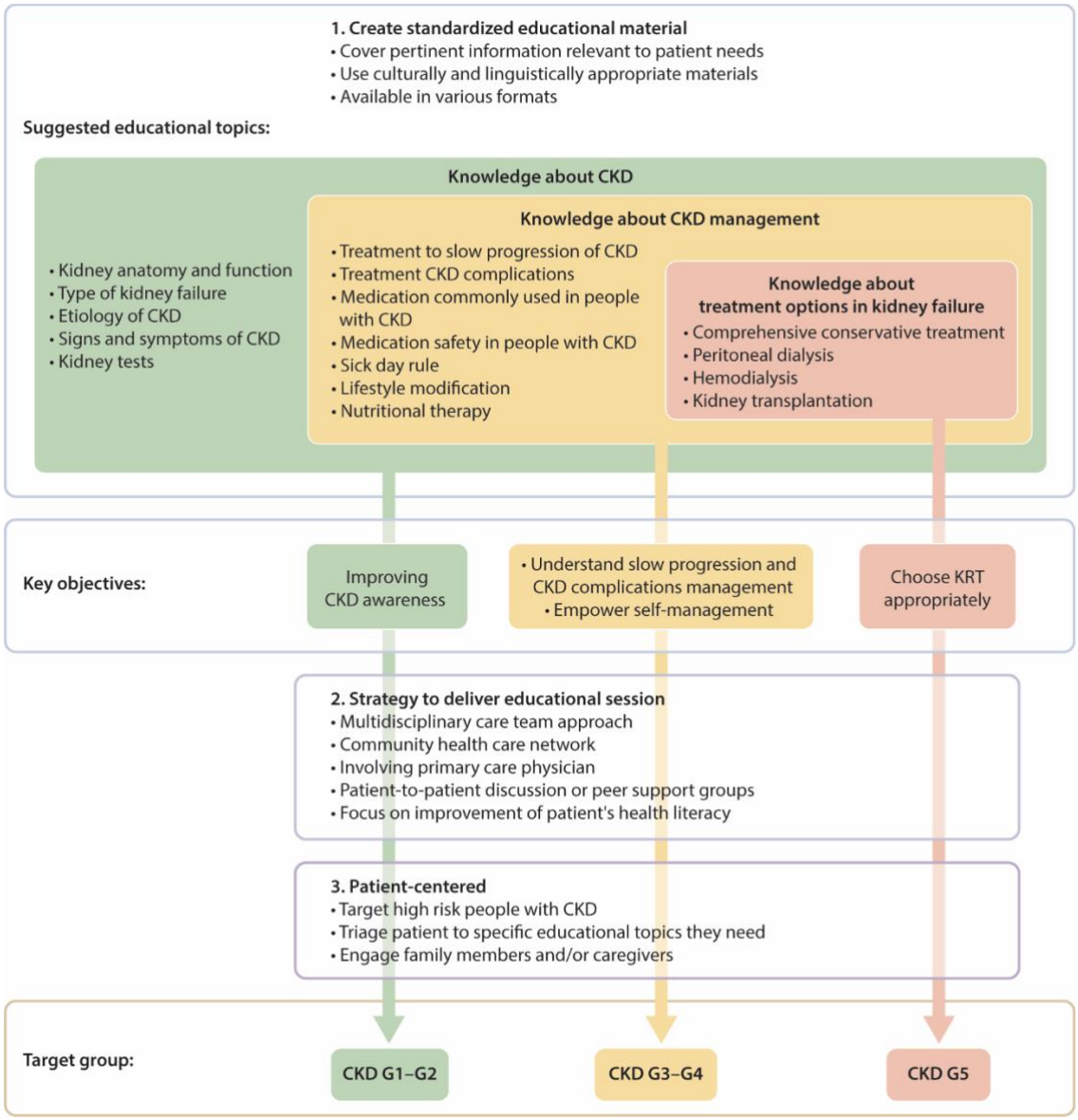


Figure 49. Strategy for effective patient education programs for people with chronic kidney disease (CKD).

Standardized educational topics should cover 3 main subject areas: knowledge about CKD, knowledge about treatment to slow progression and complications of CKD, and knowledge about the kidney failure management options.

Educational material should be written and explained clearly with plain language. Customization of information to patient needs and literacy level, and sensitive to cultural norms and needs (i.e., storytelling/videos vs. written materials). A multidisciplinary approach should be encouraged as an effective strategy for providing education. Engaging community healthcare workers and other health education providers may be an effective strategy for providing patient/carer education and empowering self-care management.[755] Targeting education to people with CKD who are at high risk of CKD progression might yield a better outcome than routine care, not only to the individual but also to the healthcare system. Engaging with family members or caregivers in a CKD education program will facilitate self-management and psychosocial support.

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.

Telehealth has been used increasingly in medicine, including nephrology, during the COVID-19 pandemic. Telehealth has the potential to augment patient care in CKD in many aspects such as, improving access to CKD care in outreach patients, increasing patient monitoring ability, helping with healthcare provider shortage, and improving patient satisfaction. Telehealth in nephrology ("Telenephrology") can be categorized into 3 main areas, (1) remote monitoring, (2) providing education, and (3) delivery of care. These have been implemented in 4 main platforms including internet web-based, smart phone applications, interactive video conferencing and wearable technology.

Remote monitoring technology has been designed to promote self-care through oversight of clinical parameters so people with CKD can monitor changes at home, such as BP, body weight or abnormal symptoms.[756, 757] This may encourage people with CKD to participate in the management of CKD.

Telehealth technologies that enhance education in people with CKD have been reported in various forms. Web-based applications are probably the most popular platform used to provide education for people with CKD and their families.[758] Systematic reviews suggest that web-based CKD materials are mostly adequate, but not written at a suitable literacy level for most people with CKD.[759, 760]

Smart phone applications have been increasingly adopted for patient education in CKD. Educational material can be installed into smartphone applications as a tool for on-demand knowledge. Moreover, smartphones applications that provide self-management support for people with CKD were reported in a pilot study.[761] The application targeted 4 key self-care parameters: monitoring BP, medication management, symptom assessment, and

tracking laboratory results. Lastly, interactive video conferencing can provide patient education simultaneously with a virtual visit.[762, 763] This strategy should not be intended to replace the clinic visit but would be helpful for dealing with any event that happens between follow-up face-to-face visits, such as follow-up of clinical symptoms after starting or adjusting medication. Examples of telehealth technologies that were studied in people with CKD are shown in Figure 50.

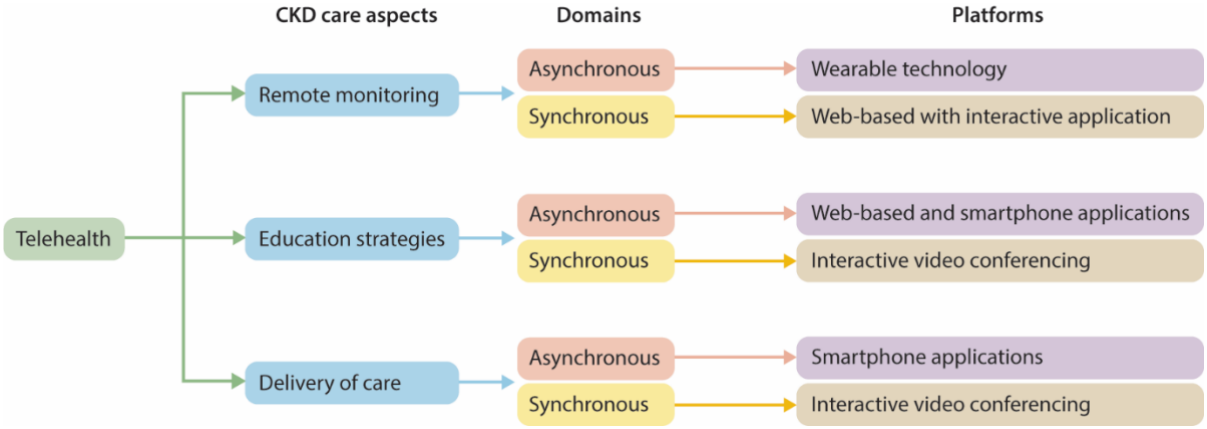


Figure 50. Telehealth technologies for people with chronic kidney disease (CKD).

Standardized and culturally appropriate protocols should be considered. While it is recognized that resources may vary across and within jurisdictions, recommendations here are based on principles of care, which should be relevant across the globe.

CKD is a complex condition that coexists with many other conditions. Therefore, models of care should be developed that integrate the complexity of the clinical conditions involved, patient-centered philosophies, and the healthcare environment. The principles of care are universal, but implementation may be customized to specific circumstances.

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 (Figure 51).

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 (Figure 51).

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

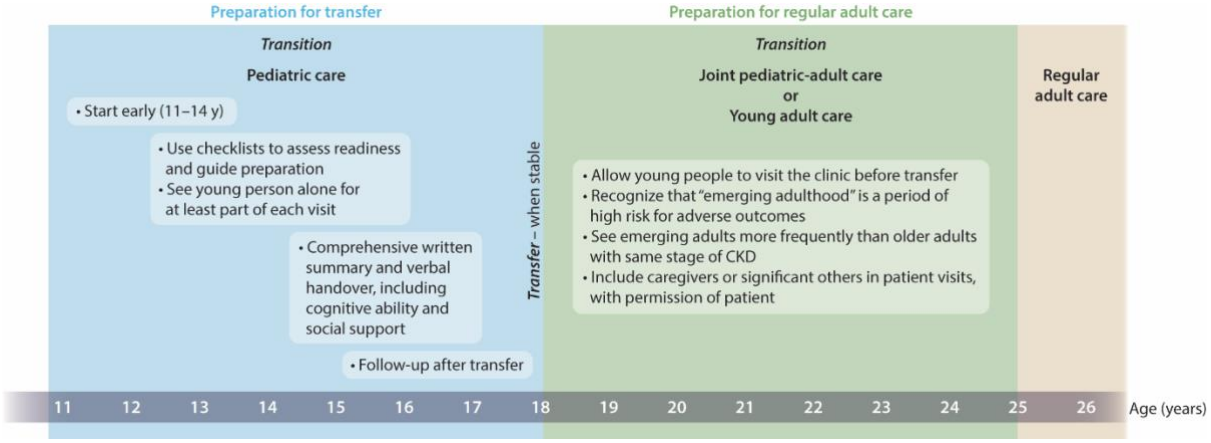


Figure 51. The process of transition from pediatric to adult care in chronic kidney disease (CKD).

While several organizations have made recommendations about transition from pediatric to adult care, there have been no randomized trials to test the effectiveness of specific approaches.[764-766] Nevertheless, there is general agreement that preparation for transfer to adult care should start as early as 11 years of age and certainly by 14 years when possible.[767] A number of tools are available to guide preparation. Checklists to assess readiness (i.e., TRxANSITION, Youth Quiz from the On Trac program, Transition Readiness Assessment Questionnaire (TRAQ), Readiness for Transition Questionnaire (RTQ), and Got Transition tools http://www.gottransition.org) are useful to identify areas of weakness.[768-771] Young people should gradually be prepared for full autonomy with medical visits. Seeing the young person alone prior to inviting caregivers into the room allows young people to practice interacting with healthcare providers independently and provides privacy for discussion of sensitive topics.

Good communication between the transferring and receiving care teams is a cornerstone of successful transitions. A comprehensive written medical summary must be provided; a verbal handover is ideal. Since childhood CKD may be associated with neurodevelopmental disabilities, a clear description of the young person's cognitive abilities, including strengths and weaknesses that may influence their ability for self-management, is critical. Information about social support available to young people is also important.

Healthcare transitions are well known to be strongly associated with adverse outcomes, including loss to follow-up. Transferring during periods of instability is ill-advised and may amplify the risk of poor outcomes.[766] To minimize the risk of loss to follow-up, pediatric care providers should follow-up with patients to ensure that they have engaged with the new care team.

Transition clinics may improve the outcomes of young people transitioning from pediatric to adult care.[772, 773] Transition clinics may be staffed exclusively by pediatric care providers and focus on preparation, or may be jointly staffed by pediatric and adult providers.[767, 774] While joint pediatric-adult clinics are viewed as ideal, their superiority has

not been demonstrated in randomized trials. Furthermore, feasibility may be limited by funding, geography, and staffing. Young people should have the opportunity to visit the adult clinic prior to transfer.

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 risk of incomplete brain development.

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 (Figure 51).

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 (Figure 51).

Even for young people without chronic illness, the interval between 14 and 25 years of age is a period of change and increasing autonomy. Young people with CKD undergoing transfer to adult care must navigate 2 transitions simultaneously: the transition of care and the larger transition from childhood to adulthood. Development of the prefrontal cortex, responsible for planning, organization, and impulse control, continues to about 25 years of age. Adult care providers must recognize that young adults constitute a high-risk population requiring special care.[775] Outcomes are poorer during this interval than at other times of life.[776] Care must reflect the fact that this is a high-risk period.

An informal visit to the new clinic setting may help in reducing stress, improving engagement, and reducing loss to follow-up.[767] In the initial years following transfer, visits should be more frequent than for older adults with the same stage of CKD to provide an opportunity for care providers establish a relationship with the young person, reduce the risk of loss to follow-up, and provide enhanced monitoring of a group at high risk of adverse outcomes. While young adults must have an opportunity to meet their care providers alone, many will continue to desire and need involvement of parents or significant others in their care. This is a normal part of development, is associated with better outcomes, and should be encouraged.[767]

Multidisciplinary young adult clinics including youth workers, social workers, and psychologists in addition to physicians and nurses may be beneficial.[772] Peer support programs have also shown promise.[776]

5.4. Timing the initiation of dialysis

Practice Point 5.4.1: Initiate dialysis based on a composite assessment of person's symptoms, quality of life, patient 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 (Table 42). This often but not invariably occurs in the GFR range between 5 and 10 ml/min per 1.73 m^2.

Symptoms or signs attributable to kidney failure (e.g., neurological signs and symptoms attributable to uremia, pericarditis, anorexia, medically resistant acid-based or electrolyte abnormalities, intractable pruritus, serositis, acid-base or electrolyte abnormalities)
Inability to control volume status or blood pressure.
Progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.

Table 42. Indications for the initiation of dialysis.

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

These statements are worded very precisely to highlight the need for KRT to address symptoms and to avoid the institution of dialysis therapy at an arbitrary number representing the degree of residual kidney function. Given the risks and benefits of KRT, as well as the potential imprecision of measurements, people with CKD need to be treated according to symptoms and signs, not simply based on a laboratory value. Data from the Initiating Dialysis Early and Late (IDEAL) RCT show no survival advantage to early start dialysis.[777] Thus, the statement as written should help the healthcare provider to balance symptoms with laboratory values in decision-making.

Secondary analyses of the IDEAL study showed no significant difference in quality of life or healthcare-related cost between early and late start dialysis groups.[777, 778] Moreover, subgroup analysis of the IDEAL study revealed no benefits on cardiac outcome in the early start dialysis group.[779] Since the IDEAL study, there were a number of large sample size observational studies with advanced statistical technique to reduce possible confounding factors and biases encountered in previous observational studies.[780-782] The overall results were consistent with the IDEAL study and showed no benefits of early start dialysis compared to late start dialysis in regard to morality and hospitalization risk (Table 43).

Factors such as availability of resources, reasons for starting dialysis, timing of dialysis initiation, patient education and preparedness, dialysis modality and access, as well as varied "country-specific" factors significantly affect a person's experiences and outcomes. As the burden of kidney failure has increased globally, there has also been a growing recognition of the importance of patient involvement in determining the goals of care and

decisions regarding treatment. It is important to move away from a “one-size-fits-all” approach to dialysis and provide more individualized or personalized care.

The availability of resources for formal multidisciplinary teams, educational materials, and access to specialized counselling for diet, advance directives, access planning, and preemptive transplantation varies around the world. These statements are proposed so that “best practices” can be documented or aspired to. The need for education, planning, and appropriate expertise for the management of this patient group is internationally relevant. The methods, frequency, and tools with which this can be accomplished will be region specific.

There is a need to focus on regular symptom assessment as part of CKD review in those with lower eGFR values. Individual assessment and availability of resources will dictate specific timing of therapies. Healthcare providers should be aware of the impact of early dialysis start on quality of life before recommending this strategy to people with CKD.

Study	Study design	Comparison/study populations	Outcomes	Results
Cooper BA *et al*. 2010: IDEAL study[777]	RCT	Late start group ($eGFR_{CG}$ 5–7 ml/min per 1.73 m^2) Early start group ($eGFR_{CG}$ 10–14 ml/min per 1.73 m^2)	Mortality	Hazard ratio with early initiation, 1.04; 95% CI; 0.83–1.30; P=0.75
Harris A *et al*. 2011[778]	*Post hoc* analysis of IDEAL study	Late start group ($eGFR_{CG}$ 5–7 ml/min per 1.73 m^2) Early start group ($eGFR_{CG}$ 10–14 ml/min per 1.73 m^2)	Cost Quality of life	No statistical difference between early start vs. late start group
Whalley GA *et al*. 2013[779]	*Post hoc* analysis of IDEAL study	Late start group ($eGFR_{CG}$ 5–7 ml/min per 1.73 m^2) Early start group ($eGFR_{CG}$ 10–14 ml/min per 1.73 m^2)	Change in cardiac structure and function (LVMI, LVEF, LAVI) over 12 months and between groups	No statistically significant change in cardiac structure and function over 12 months follow up. No statistically significant difference in cardiac structure and function between 2 groups
Rosansky SJ *et al*. 2011[782]	Observational study	81,176 subjects with kidney failure aged 20–64 years, without diabetes, and with no comorbidity other than hypertension	1-year mortality	The unadjusted 1-year mortality by MDRD eGFR at dialysis initiation ranged from 6.8% in the reference group (eGFR <5.0 ml/min per 1.73 m^2) to 20.1% in the highest eGFR group (≥15.0 ml/min per 1.73 m^2).
Nacak H *et al*. 2016[781]	Observational study	35,665 subjects with serum albumin concentrations of 3.5 g/dl or higher prior to hemodialysis initiation	1-year mortality	1-year mortality was 4.7%. In this group, the adjusted HR for mortality was 1.27 for eGFR 5.0–9.9 ml/min per 1.73 m^2, 1.53 for eGFR 10.0–14.9 ml/min per 1.73 m^2, and 2.18 for GFR ≥15.0 ml/min per 1.73 m^2 compared with the reference group of GFR <5.0 ml/min per 1.73 m^2.
Fu EL *et al*. 2021[780]	Observational study	10,290 people with CKD G4–G5; compare dialysis initiation strategies with eGFR values ranging between 4 and 19 ml/min per 1.73 m^2 and use an eGFR between 6 and 7 ml/min per 1.73 m^2 as the reference group	5-year mortality	The maximum 5-year mortality risk reductions were 5.1% (for $eGFR_{15-16}$ vs. $eGFR_{6-7}$), translating into a better survival of only 1.6 months over a 5-year period at the expense of starting dialysis 4 years earlier

Table 43. Studies examining the timing of dialysis in people with chronic kidney disease (CKD). CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; IDEAL, Initiating Dialysis Early and Late; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MDRD, Modification of Diet in Renal Disease; RCT, randomized controlled trial

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 eGFR 5–15 ml/min per 1.73 m^2.

In children, poor growth can also be a reason to initiate dialysis. The decision to start dialysis should be reached in discussion with the child (if age appropriate), their caregivers, and their healthcare providers. Medical and psychosocial preparations for the initiation of dialysis should begin well before dialysis is required.

Deferred initiation should not imply deferred preparation, and early discussions regarding medical and psychosocial preparation for the initiation of dialysis should not be delayed (e.g., placement of dialysis access, dialysis modality selection, advance care planning, assistance with home therapies).

In children, studies from the US Renal Data System (USRDS) and the European Society of Paediatric Nephrology (ESPN) found no benefit from starting dialysis early.[783, 784] Of 15,000 incident children on dialysis in the USRDS, the mortality risk was 36% higher for those with eGFR >10 ml/min per 1.73 m^2 compared with those with lower eGFR at dialysis initiation.[784] Mortality risk increased in those starting dialysis with eGFR <5 and ≥12 ml/min per 1.73m^2, with a greater risk in people 6 years and older.[785] A retrospective ESPN study of nearly 3000 children found mortality did not differ when dialysis was started with an eGFR above or below 8 ml/min per 1.73 m^2.[783] This observational data may be confounded by indication bias.

5.5. 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: Enable 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.

These statements are intended to highlight the importance of supportive care and the need for comprehensive conservative care processes and resources in the care of this complex patient group. The term supportive care in nephrology means care that is focused on improving the HRQoL for people with CKD at any severity or age and can be provided along with therapies intended to prolong life, such as dialysis.[716] Whereas, comprehensive conservative management is usually referred to as active medical management in people with kidney failure who choose not to have KRT. There are 3 distinct groups of people with kidney failure who receive comprehensive conservative care because provision of supportive care differs for each.[786] Descriptions of each group are shown in Table 44.

Category	Description
Receiving conservative care	Conservative care that is chosen or medically advised/
Choice-restricted conservative care	Conservative care for person in whom resource constraints prevent or limit access to KRT; therefore, a choice for conservative care cannot be recognized.
Unrecognized CKD G5	CKD is present but has not been recognized or diagnosed; therefore, a choice for conservative care cannot be recognized.

Table 44. People with kidney failure who receive comprehensive conservative care. CKD, chronic kidney disease; KRT, kidney replacement therapy

There is increasing recognition that provision of organized care to those who are dying or choose to not pursue KRT is of value to people with CKD and their families. Healthcare providers involved in caring for these people should be alerted to this need.

Comprehensive conservative care is an alternative treatment to KRT. This is planned, holistic, person-centered care that includes the full integration of comprehensive conservative care including the following:

- Detailed communication including estimating prognosis and advance care planning,
- Shared decision-making,
- Active symptom assessment and management,
- Psychological, social, family, cultural, and spiritual support,
- Interventions to delay progression and minimize risks of adverse events or complications, but not include dialysis.

Evaluating the prognosis of each person with CKD is very important because each person has a different disease progression pattern. Patient prognosis is the key information for shared decision-making in CKD G5 which requires unbiased information on survival and

person-centered outcomes known to matter to people with CKD: quality of life, symptom burden, and support from family and healthcare providers. Shared decision-making helps healthcare providers, people with CKD, and family members to reach agreement on the treatment direction that is appropriate with the person's values and preferences and family goals. This process should be done in a culturally appropriate way with consideration of appropriate health literacy.

As CKD progresses, the person with CKD will experience more symptoms and complications related to CKD. Therefore, active symptom assessment and management are the key components of comprehensive conservative care in CKD G5. Assessing a person's symptoms on a regular basis helps redirect management toward a person's values and preferences and family goals. There is limited evidence for selecting treatment strategies due to the complexity of CKD and differences in people and the considerable variation in the management strategies for different symptoms. Intervention to delay progression of CKD is still an important component of comprehensive conservative care in both CKD related aspects (maintain residual kidney function and reduce cardiovascular morbidity) and psychospiritual aspects (the person and their family members do not feel that active CKD treatment is discontinued).

Advanced care planning (ACP) is a process under the comprehensive conservative care umbrella that involves understanding, communication, and discussion between a person with CKD, the family, caregiver, and healthcare providers for the purpose of clarifying preferences for end-of-life care. End-of-life care is the treatment during the phase where death is inevitable. It focuses on quality of life not quantity of lifetime. Functional and cognitive decline that may happen along with CKD progression results in difficult end-of-life conversations involving people with CKD, families, and healthcare providers. Therefore, an integrated approach to timely ACP and palliative care spanning the continuum of CKD care is needed. End-of-life care is underutilized in management of people with CKD G5 due to inadequate education during nephrology training leading to poor end-of-life care discussions with the person. The overall concept of supportive care, comprehensive conservative care, and end-of-life care is shown in Figure 52.

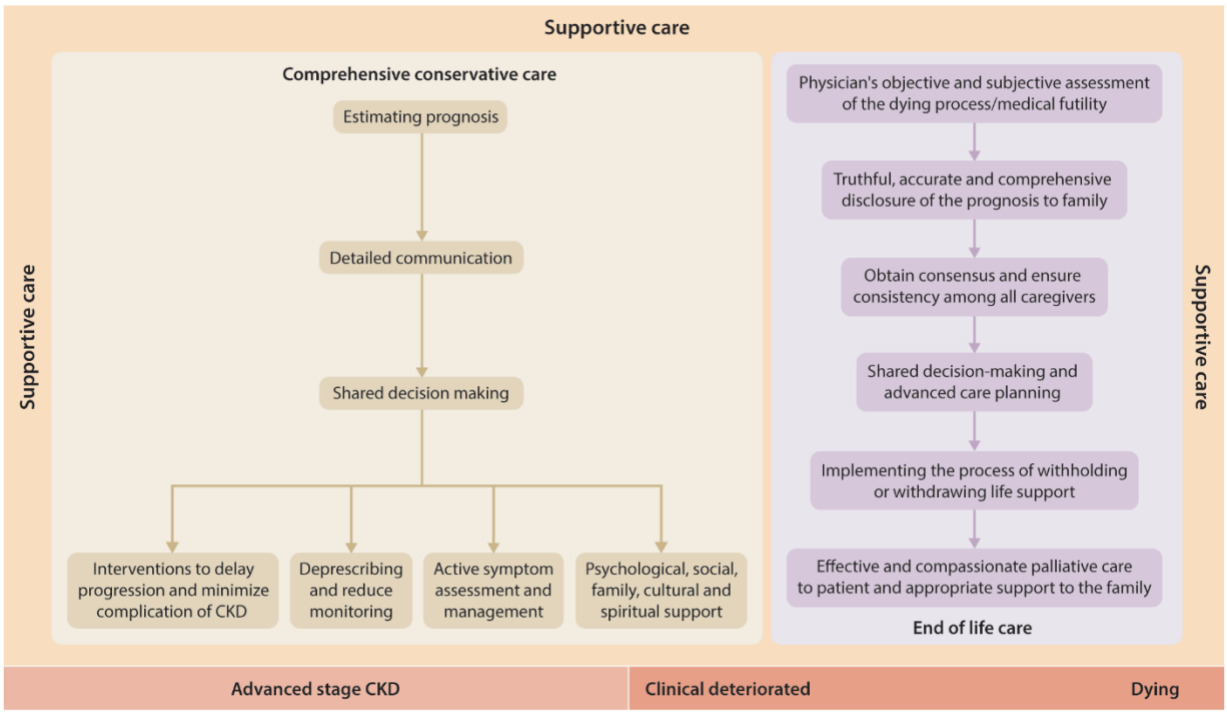


Figure 52. Relationship between supportive care, comprehensive conservative care, and end-of-life care. CKD, chronic kidney disease

In different societies or cultural areas, the form and structure of this care may vary tremendously, and families or religious organizations may be able to deliver suitable and sensitive care. The details here are listed not to be prescriptive but rather to articulate the best practices in communities where resources may be available and to serve a construct to review in those locations where resources are more limited.

METHODS FOR GUIDELINE DEVELOPMENT

AIM

The aim of this project was to update the *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*.[1] The guideline development methods are described below.

OVERVIEW OF THE PROCESS

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Table S2 and S3)[787, 788] and have been reported in accordance with the AGREE II reporting checklist.[789] The processes undertaken for the development of the KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of CKD are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope of the guideline
- Developing and registering protocols for systematic reviews
- Implementing literature search strategies to identify the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and risk of bias assessment of included studies
- Conducting evidence synthesis, including meta-analysis where appropriate
- Assessing the certainty of the evidence for each critical outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the overall certainty of the evidence and other considerations
- Convening a public review of the guideline draft in June 2023
- Updating systematic reviews
- Amending the guideline based on the external review feedback and updated systematic reviews
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT

KDIGO and the Co-Chairs assembled a Work Group with expertise in pediatric, adult, and geriatric nephrology, including both dialysis and transplant specialists; primary care; internal medicine; dietetics; nursing; women's health; clinical trials; epidemiology; medical decision-making; and public health; as well as people living with CKD were engaged. Johns Hopkins University with expertise in nephrology, evidence synthesis, and guideline development was contracted as the ERT and was tasked with conducting the evidence reviews. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, risk of bias assessment, evidence synthesis and meta-analysis, grading the certainty of the evidence per

critical outcome, and grading the overall certainty of the evidence for the recommendations. The Work Group was responsible for writing the recommendations and the underlying rationale, grading the strength of the recommendations, and developing practice points.

Defining scope and topics and formulating key clinical questions

The KDIGO 2012 CKD guideline was reviewed by the Co-Chairs to identify topics to be included in the 2023 guideline. Scoping reviews of these topics were conducted by the ERT to provide an overview of the available evidence base and to identify existing relevant systematic reviews.

The Risk of Bias in Systematic Reviews (ROBIS) tool was used to assess the risk of bias of the existing reviews. When high-quality systematic reviews were identified during the scoping reviews, the ERT conducted an updated search based on the existing review and extracted information from the newly identified studies. This information was added to the existing review data and analyzed as appropriate.

For topics that did not map to current high-quality reviews, *de novo* systematic reviews were undertaken. Protocols for each review were developed by the ERT and reviewed by the Work Group. Protocols were registered on PROSPERO (https://www.crd.york.ac.uk/prospero/). Systematic reviews were conducted in accordance with current standards, including those from the Cochrane Handbook.[790]

Details of the Population, Intervention, Comparator, Outcome and Study design (PICOS) of the questions are provided in Table 45. Information about existing reviews that were used is included in these tables.

For some topics not predefined in the Scope of Work, the ERT extracted certainty of evidence from existing high-quality systematic reviews, as available. Details of the PICOS for these questions are also provided in Table 45.

Chapter 1	Evaluation of CKD
Clinical question	**What is the diagnostic and prognostic benefit and safety of kidney biopsy among people with chronic kidney disease (CKD)?**
Population	Adults and children with suspected or diagnosed CKD
Intervention (index test)	Native kidney biopsy
Comparator	For studies evaluating diagnostic or prognostic benefit, clinical or standard diagnosis or prognosis For studies evaluating safety, no comparator
Outcomes	Critical outcomes: mortality, perirenal hematoma (perinephric hematoma), retroperitoneal hemorrhage Other outcomes: diagnostic and prognostic benefit, macroscopic hematuria, transfusion, need for embolization, nephrectomy, AKI, major complications
Study design	Non-comparative studies, pre-post studies
Existing systematic review used for hand-searching	Poggio ED, McClelland RL, Blank KN, et al. Systematic Review and Meta-Analysis of Native Kidney Biopsy Complications. Clinical journal of the American Society of Nephrology : CJASN. 2020 Nov 6;15(11):1595-602. doi: 10.2215/cjn.04710420. PMID: 33060160.
SoF tables	Supplementary Table S4
Search date	September 2022
Citations screened/included studies	1486/66
Clinical question	**What is the diagnostic accuracy of eGFR based on measurements of cystatin C, creatinine, or their combination compared to mGFR among people with and without CKD?**
Population	Adults and children with or without CKD
Intervention (index test)	eGFR based on measurements of cystatin C (eGFRcys), creatinine (eGFRcr), cystatin C and creatinine (eGFRcr-cys)
Comparator	mGFR (using urinary or plasma clearance of exogenous filtration marker)
Outcomes	Critical outcomes: measurement bias (eGFR – mGFR), accuracy (P_{30} & P_{15}) Other outcomes: probability of being classified in each eGFR category
Study design	Cross-sectional
Existing systematic reviews	None
SoF tables	Supplementary Table S23
Search date	August 2022
Citations screened/included studies	1848/47
Clinical question	**In children and young adults with suspected or diagnosed CKD, what is the accuracy of albumin-to-creatinine ratio (ACR) and protein-to-creatinine ratio (PCR) compared to 24-hour excretion of albumin or protein?**
Population	Children and young adults (age <25 years) with suspected or diagnosed CKD
Intervention (index test)	ACR, PCR
Comparator	Albuminuria or proteinuria determined from 24-hour urine collection
Outcomes	Outcomes: Median IQR or difference between intervention and comparison, sensitivity and specificity for detection and diagnosis of significant proteinuria

Study design	Prospective, observational studies
Existing systematic review used for handsearching	NICE Evidence Reviews Collection. Evidence review for the accuracy of albumin: creatinine ratio versus protein creatinine ratio measurements to quantify proteinuria in children and young people with CKD: Chronic kidney disease: Evidence review B. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE; 2021.
SoF tables	No summary of findings table
Search date	July 2022
Citations screened/included studies	485/0 Supplementary Figure S3
Clinical question	**What is the diagnostic accuracy and reproducibility of point-of-care (POC) blood creatinine compared to laboratory-based tests among people with suspected or diagnosed CKD?**
Population	Adults and children
Intervention (index test)	Quantitative internationally standardized POC creatinine tests
Comparator	Laboratory-based methods for measuring SCr
Outcomes	Critical outcomes: measurement bias, analytical sensitivity (limit of detection), analytical variability (coefficient of variation)
Study design	Cross-sectional
Existing systematic reviews used for hand-searching	Point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast. 2019; 38. Available at: www.nice.org.uk/guidance/dg37 13 November 2019. Corbett M, Duarte A, Llewellyn A, et al. Point-of-care creatinine tests to assess kidney function for outpatients requiring contrast-enhanced CT imaging: systematic reviews and economic evaluation. Health technology assessment (Winchester, England). 2020;24(39):1-248.
SoF tables	No summary of findings table
Search date	January 2023
Citations screened/included studies	986/55 Supplementary Figure S4
Clinical question	**What is the diagnostic accuracy of quantitative and semi-quantitative protein or albumin urine dip stick tests compared to laboratory-based tests among people with suspected or diagnosed CKD?**
Population	Adults and children
Intervention (index test)	Machine-read quantitative or semi-quantitative protein or albumin urine dip stick tests
Comparator	Laboratory-based methods for measuring urinary protein or albumin (e.g., 24-hour urinary sample, spot urine ACR or PCR)
Outcomes	Critical outcomes: measurement bias, analytical sensitivity (limit of detection), analytical variability (coefficient of variation), analytic specificity (or numbers to calculate) Other outcomes: probability of being classified in each albuminuria or proteinuria stage
Study design	Cross-sectional
Existing systematic reviews for hand-searching	McTaggart MP, Newall RG, Hirst JA, et al. Diagnostic accuracy of point-of-care tests for detecting albuminuria: a systematic review and meta-analysis. Annals of internal medicine. 2014;160(8):550-557.
SoF tables	Supplementary Table S24
Search date	July 2022

Citations screened/included studies	2184/65 Supplementary Figure S5
Chapter 3	**Delaying CKD progression and managing its complications**
Clinical question	**What is the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) compared with placebo, usual care, or an active comparator among people with CKD but not type 2 diabetes (T2D) in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD but not diabetes; subgroup of people with heart failure
Intervention	SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, tofogliflozin)
Comparator	Active comparator (e.g., another glucose-lowering agent), placebo or usual care
Outcomes	Critical outcomes: kidney failure (including CKD progression), all-cause hospitalizations Other outcomes: mortality, change in eGFR (including acute changes), complications of CKD, adverse events
Study design	Randomized controlled trials (RCTs)
Existing systematic reviews for hand-searching	Kamdar A, Sykes R, Morrow A, et al. Cardiovascular outcomes of glucose lowering therapy in chronic kidney disease patients: a systematic review with meta-analysis. Reviews in cardiovascular medicine. 2021 Dec 22;22(4):1479-90. doi: 10.31083/j.rcm2204152. PMID: 34957787. Li N, Zhou G, Zheng Y, et al. Effects of SGLT2 inhibitors on cardiovascular outcomes in patients with stage 3/4 CKD: A meta-analysis. PloS one. 2022;17(1):e0261986. doi: 10.1371/journal.pone.0261986. PMID: 35020750. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney international. 2022 Nov;102(5s):S1-s127. doi: 10.1016/j.kint.2022.06.008. PMID: 36272764.
Existing systematic review data included	Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet (London, England). 2022 Nov 19;400(10365):1788-801. doi: 10.1016/s0140-6736(22)02074-8. PMID: 36351458.
SoF tables	Supplementary Table S5
Search date	Kamdar 2021: April 2021; Li 2022: August 27, 2021; NDPH 2022: September 2022; KDIGO 2022: December 2021
Citations screened/included studies	252/2 Supplementary Figure S6
Clinical question	**What is the effect of mineralocorticoid receptor agonists (MRAs) compared with placebo, usual care, or an active comparator among people with CKD but not T2D in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD but not diabetes
Intervention	Steroidal MRAs (canrenone, eplerenone, spironolactone); non-steroidal MRAs (esaxerenone, finerenone)
Comparator	Active comparator, placebo, or usual care
Outcomes	Critical outcomes: kidney failure, all-cause hospitalizations Other outcomes: mortality, progression of CKD, complications of CKD, adverse events
Study design	RCTs

Existing systematic review data included	Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2020 Oct 27;10(10):Cd007004. doi: 10.1002/14651858.CD007004.pub4. PMID: 33107592.
SoF tables	Supplementary Table S7
Search date	January 2020
Citations screened/included studies	106/19 Supplementary Figure S8
Clinical question	**What is the effect of MRAs compared with placebo, usual care, or an active comparator among people with CKD and T2D in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD and diabetes; subgroup of people with heart failure
Intervention	Steroidal MRAs (canrenone, eplerenone, spironolactone); non-steroidal MRAs (esaxerenone, finerenone)
Comparator	Active comparator, placebo, or usual care
Outcomes	Critical outcomes: kidney failure, all-cause hospitalizations
Study design	RCTs
Existing systematic reviews	KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022 Nov;102(5s):S1-s127. doi: 10.1016/j.kint.2022.06.008. PMID: 36272764.
SoF tables	Supplementary Table S8
Search date	December 2021
Citations screened/included studies	106/?
Clinical question	**What is the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RA) compared with placebo, usual care, or an active comparator among people with CKD but not T2D in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD but not diabetes
Intervention	GLP-1 RA (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide)
Comparator	Active comparator (e.g., another glucose-lowering agent), placebo or usual care
Outcomes	Critical outcomes: kidney failure, all-cause hospitalizations
Study design	RCTs
Existing systematic reviews for hand-searching	Kamdar A, Sykes R, Morrow A, et al. Cardiovascular outcomes of glucose lowering therapy in chronic kidney disease patients: a systematic review with meta-analysis. Reviews in cardiovascular medicine. 2021 Dec 22;22(4):1479-90. doi: 10.31083/j.rcm2204152. PMID: 34957787. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney international. 2022 Nov;102(5s):S1-s127. doi: 10.1016/j.kint.2022.06.008. PMID: 36272764.
SoF tables	No summary of findings table
Search date	Kamdar 2021: March 2021; KDIGO 2022: December 2021
Citations screened/included studies	65/0 Supplementary Figure S9

Clinical question	**What is the effect of GLP-1 RA compared with placebo, usual care, or an active comparator among people with CKD and T2D in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD and diabetes; subgroup of people with heart failure
Intervention	GLP-1 RA (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide)
Comparator	Active comparator (e.g., another glucose-lowering agent), placebo or usual care
Outcomes	Critical outcomes: kidney failure, all-cause hospitalizations
Study design	RCTs
Existing systematic reviews	Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney international. 2022 Nov;102(5s):S1-s127. doi: 10.1016/j.kint.2022.06.008. PMID: 36272764.
SoF tables	No summary of findings table
Search date	December 2021
Citations screened/included studies	23
Clinical question	**What is the effect of uric acid-lowering therapy compared with placebo, usual care, or an active comparator among people with CKD and hyperuricemia in terms of mortality, progression of CKD, complications of CKD, and adverse events?**
Population	Adults and children with CKD and hyperuricemia
Intervention	Allopurinol, benzbromarone, febuxostat, lesinurad, oxupurinol, pegloticase, probenecid, rasburicase, sylfinpyrazone, topiroxostat
Comparator	Active comparator (e.g., another uric acid-lowering therapy), placebo, or usual care
Outcomes	Critical outcomes: kidney failure, cutaneous reactions, hypersensitivity, hepatotoxicity Other outcomes: all-cause mortality, cardiovascular mortality, eGFR, ACR, cardiovascular events, gout
Study design	RCTs
Existing systematic reviews for hand-searching and updating	Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. The Cochrane database of systematic reviews. 2017 Oct 30;10(10):Cd009460. Doi: 10.1002/14651858.CD009460.pub2. PMID: 29084343.
SoF tables	Supplementary Table S9
Search date	July 2022
Citations screened/included studies	1588/25 Supplementary Figure S10
Clinical question	**What is the effect of aspirin compared to placebo in terms of the primary prevention of cardiovascular disease (CVD) and safety among people with CKD?**
Population	Adults and children with CKD at risk for CVD (i.e., people must not have established CVD[†])
Intervention	Aspirin
Comparator	Placebo
Outcomes	Critical outcomes: incident CVD events, bleeding (intracranial hemorrhage, major extracranial hemorrhage, clinically relevant non-major bleeding)

Study design	RCTs
Existing systematic reviews for hand-searching and updating	Pallikadavath S, Ashton L, Brunskill NJ, et al. Aspirin for the primary prevention of cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. European journal of preventive cardiology. 2022 Feb 3;28(17):1953-60. Doi: 10.1093/eurjpc/zwab132. PMID: 34448849.
SoF tables	Supplementary Table S10
Search date	August 2022
Citations screened/ included studies	2293/5 Supplementary Figure S11
Clinical question	**What are the effects of angiography or coronary revascularization compared to medical treatment among people with CKD and ischemic heart disease in terms of mortality, CVD events, kidney failure, and acute kidney injury (AKI)?**
Population	Adults and children with CKD and ischemic heart disease
Intervention	Angiography or coronary revascularization
Comparator	Medical treatment
Outcomes	Critical outcomes: all-cause mortality, CVD mortality, CVD events (including composite cardiovascular events, myocardial infarction, heart failure), kidney failure, AKI Other outcomes: patient-reported outcomes
Study design	RCTs
Existing systematic reviews	None
SoF tables	Supplementary Table S11
Search date	August 2022
Citations screened/ included studies	3284/5 Supplementary Figure S12
Clinical question	**What are the effects of non-vitamin K antagonist oral anticoagulants (NOACs) (also known as direct-acting oral anticoagulants [DOACs]) with or without warfarin compared to placebo or warfarin alone among people with CKD and atrial fibrillation in terms of stroke and bleeding risks?**
Population	Adults and children with CKD and atrial fibrillation
Intervention	NOAC/DOAC (dabigatran, apixaban, edoxaban, rivaroxaban) with warfarin; NOAC/DOAC alone
Comparator	Warfarin, placebo
Outcomes	Critical outcomes: stroke (including TIA), bleeding (including intracranial hemorrhage, major bleeding, clinically-relevant non-major bleeding)
Study design	RCTs
Existing systematic reviews for hand-searching and updating	Kimachi M, Furukawa TA, Kimachi K, et al. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. The Cochrane database of systematic reviews. 2017 Nov 6;11(11):Cd011373. Doi: 10.1002/14651858.CD011373.pub2. PMID: 29105079.
SoF tables	Supplementary Table S12 and S13
Search date	August 2022

Citations screened/ included studies	3546/7 Supplementary Figure S13

Table 45. Clinical questions and systematic review topics in PICOM format. ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; BMI, body mass index; DDD, dense deposit disease; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MPGN, membranoproliferative glomerulonephritis; PICOM, Population, Intervention, Comparator, Outcomes, Methods; RCT, randomized controlled trial; SCr, serum creatinine; SoF, summary of findings

Literature searches and article selection

Searches for RCTs were conducted on PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) and searches for diagnosis/prognosis studies were conducted on PubMed, Embase, and CINAHL. For topics with available existing reviews, the review was used and an updated search was conducted. The search strategies are provided in Appendix A: Supplementary Table Sl.

To improve efficiency and accuracy in the title/abstract screening process and to manage the process, search results were uploaded to a web-based screening tool, PICO Portal (www.picoportal.net). PICO Portal uses machine learning to sort and present first those citations most likely to be promoted to full-text screening. The titles and abstracts resulting from the searches were initially screened independently by 2 members of the ERT. One screener was used when the recall rate of citations promoted to full text screening reached at least 90% and then title and abstract screening was stopped when the recall rate of citations promoted to full-text was at least 95%. Citations deemed potentially eligible at the title and abstract stage were screened independently by 2 ERT members at the full-text level. At both title/abstract and full-text screening disagreements about eligibility were resolved by consensus, and, as necessary through discussion amongst the ERT members.

Search dates, number of citations that were screened, and number of eligible studies are included in Table 45. Supplemental Figures S1 through S21 include PRISMA diagrams for each systematic review.

A total of 17,904 citations were screened. Of these, 63 RCTs and 235 non-randomized studies were included in the evidence review (Figure 53).

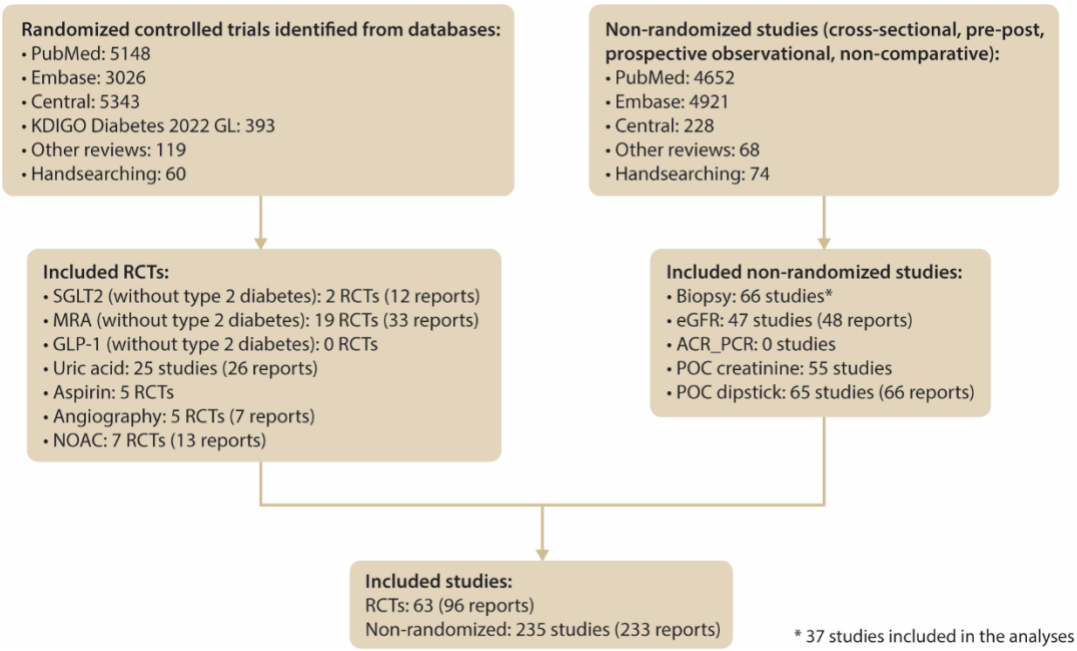


Figure 53. Search yield and study flow diagram.

Data extraction

Data extraction, from studies and existing systematic reviews, was performed by a member of the ERT and confirmed by a second member of the ERT. Any differences among members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Risk of bias of studies and systematic reviews

The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, the Cochrane Risk of Bias 2 tool was used to assess risk of bias for RCTs based on the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.[791]

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess study limitations of diagnostic studies based on the following items:[792]

- Could the selection of patients have introduced bias (patient selection)?
- Could the conduct or interpretation of the index test have introduced bias (index test)?
- Could the reference standard, its conduct, or its interpretation have introduced bias (reference standard)?
- Could the patient flow have introduced bias (flow and timing)?
- Applicability
- Are there concerns that the included patients and setting do not match the review question?

- Are there concerns that the index test, its conduct, or interpretation differ from the review question?
- Are there concerns that the target condition as defined by the reference standard does not match the question?

The Risk of Bias in Systematic Reviews (ROBIS) tool was used to assess risk of bias of systematic reviews based on study eligibility criteria, identification and selection of studies, data collection and study appraisal, overall risk of bias.[793]

All risk of bias assessments were conducted independently by 2 members of the ERT, with disagreements resolved by internal discussion and consultation with a third ERT member, as needed.

Evidence synthesis and meta-analysis

Measures of treatment effect – For dichotomous outcomes, a pooled effect estimate was calculated of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[794] For continuous outcomes, a standardized mean difference was calculated by using a random-effects model with the DerSimonian and Laird formula.[794]

Data synthesis – Meta-analysis was conducted if there were 2 or more studies that were sufficiently similar with respect to key variables (population characteristics, study duration, comparisons).

We combined studies of interventions in the same class when reporting outcomes. If there was substantial heterogeneity (I^2 >50%) in pooled estimates for any outcome, we stratified by the type of intervention before conducting the pooled analyses.

Pooled sensitivity and specificity was calculated using a random-effects model in studies addressing biopsy diagnosis and prognosis using the Freeman-Tukey double arcsine transformation to calculate the pooled estimate.[795] The binomial exact method to calculate the confidence intervals was used.[796]

Assessment of heterogeneity – Heterogeneity among the trials for each outcome was tested using a standard χ^2 test using a significance level of $\alpha \leq 0.10$. Heterogeneity was also assessed with an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. A value greater than 50% was considered to indicate substantial heterogeneity.[797]

Grading the certainty of the evidence and the strength of a guideline recommendation

The certainty of evidence for each critical outcome was assessed by the ERT using the GRADE approach.[798, 799] For outcomes based on data from RCTs, the initial grade for the certainty of the evidence is considered to be high. The certainty of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, outcomes measured in trials, and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size,[800] low event rates in either arm, confidence intervals that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[800] The final grade for the certainty of the evidence for an outcome could be high (A), moderate (B), low (C), or very low (D) (Tables 46 and 47).

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain and often it will be far from the true effect.

Table 46. Classification for quality and certainty of the evidence.

<table>
<tr><th>Study design</th><th>Staring grade of the quality of the evidence</th><th>Step 2 – Lower grade</th><th>Step 3 – raise grade for observational studies</th></tr>
<tr><td rowspan="2">RCTs</td><td>High</td><td rowspan="3">Study limitations:
-1 serious
-2 very serious
Inconsistency:
-1 serious
-2 very serious
Indirectness:
-1 serious
-2 very serious
Imprecision:
-1 serious
-2 very serious
Publication bias:
-1 serious
-2 very serious</td><td rowspan="3">Strength of association
+1 large effect size (e.g., <0.5 or >2)
+2 very large effect size (e.g., <0.2 or >5)

Evidence of a dose-response gradient

All plausible confounding would reduce the demonstrated effect</td></tr>
<tr><td>Moderate</td></tr>
<tr><td rowspan="2">Observational studies</td><td>Low</td></tr>
<tr><td>Very low</td></tr>
</table>

Table 47. GRADE system for grading quality of evidence. RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation

Summary of findings (SoF) tables

Summary of findings tables were developed using GRADEpro (https://www.gradepro.org/). The SoF tables include a description of the population, intervention, and comparator and, where applicable, the results from the data synthesis as relative and absolute effect estimates. The grading of the certainty of the evidence for each critical outcome is also provided in these tables. The SoF tables are available in the Appendix C and Appendix D of the Data Supplement published alongside the guideline or at https://kdigo.org/guidelines/ckd-evaluation-and-management/.

Updating and developing the guideline statements

Recommendations from the *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* were considered in the context of new evidence by the Work Group Co-Chairs and Work Group members, and updated as appropriate.[1] Practice points were not yet proposed as a separate category in 2012, so the KDIGO 2023 Work Group considered the following options: where new evidence did not suggest a change to graded recommendations, the statements were retained as graded recommendations; graded recommendations were updated where appropriate based on new evidence; existing recommendations that fit the criteria for practice points were rewritten as practice points, and new guideline statements (both recommendations and practice points) were generated for new clinical questions from the 2023 update.

Grading the strength of the recommendations

The strength of a recommendation was graded by the Work Group as Level 1 or Level 2 (Table 48). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and other considerations (Table 49).

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Table 48. KDIGO nomenclature and description for grading recommendations.

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low- or very low-quality evidence will warrant a strong recommendation.
Values and preferences	The more variability or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, where possible, or were assessed by the judgment of the Work Group, when robust evidence was not identified.
Resources and other costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Table 49. Determinants of the strength of recommendation.

Balance of benefits and harms – The Work Group determined the anticipated net health benefit on the basis of expected benefits and harms across all critical outcomes from the underlying evidence review.

The overall certainty of the evidence – The overall certainty of the evidence for each recommendation is determined by the certainty of evidence for critical outcomes. In general, the overall certainty of evidence is dictated by the critical outcome with the lowest certainty of evidence.[800] This could be modified based on the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded high (A), moderate (B), low (C), or very low (D) (Table 47).

Patient values and preferences – The Work Group included 2 people living with CKD. These members' unique perspectives and lived experience, in addition to the Work Group understanding of patient preferences and priorities, informed decisions about the strength of the recommendations. A systematic review of qualitative studies on patient priorities and preferences was not undertaken for this guideline.

Resources and other costs – Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.[801] The following resources were considered: direct healthcare costs, non-healthcare resources (such as transportation and social services), informal caregiver resources (e.g., time of family and caregivers), and changes in productivity. No formal economic evaluations, including cost-effectiveness analysis, were conducted.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help healthcare providers better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care and supplement recommendations. These were developed when no formal systematic evidence review was undertaken or there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, and they may be based on limited evidence. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1, "we recommend" or Level 2, "we suggest") and the overall certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Quality of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may also support a practice point.

Limitations of the guideline development process

Two people living with diabetes and CKD were members of the Work Group and provided invaluable perspectives and lived experiences for the development of these guidelines. However, in the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, no economic evaluations were undertaken.

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

FINANCIAL DISCLOSURE INFORMATION

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Speakers Bureaus: *AstraZeneca* and BI-Bayer**
Development of Educational Presentations: *AstraZeneca* and BI-Bayer**

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Navdeep Tangri, MD, PhD, FRCP(C)
Consultancy: *AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Janssen, Otsuka, Prokidney and Roche*
Grants/Grants Pending: *AstraZeneca*, Bayer*, Boehringer Ingelheim*, and Janssen**
Development of Educational Presentations: *AstraZeneca*
Stock/Stock Options: *Clinpredict, Klinrisk, Marizyme, Prokidney, Pulsedata, and Quanta*
Other: *Patent for a microfluidic device for measuring ACR at point of care*

Teerawat Thanachayanont, MD
Reported no relevant financial relationships

Ifeoma Ulasi, MBBS, FWACP, PGD, MSc
Speakers Bureaus: *AstraZeneca and Boehringer Ingelheim*

Germaine Wong, MD, PhD
Reported no relevant financial relationships

Chih-Wei Yang, MD
Reported no relevant financial relationships

Luxia Zhang, MD, MPH
Grants / Grants Pending: *AstraZeneca* and Bayer**

**Monies paid to institution*

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