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KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

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KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE

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KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

This article is published as part of a supplement supported by Kidney Disease: Improving Global Outcomes (KDIGO). The development and publication of this guideline were supported by KDIGO. The opinions or views expressed in this professional education supplement are those of the authors and do not necessarily reflect the opinions or recommendations of the International Society of Nephrology or Elsevier. Dosages, indications, and methods of use for products that are referred to in the supplement by the authors may reflect their clinical experience or may be derived from the professional literature or other clinical sources. Because of the differences between *in vitro* and *in vivo* systems and between laboratory animal models and clinical data in humans, *in vitro* and animal data do not necessarily correlate with clinical results.

TABLES

FIGURES

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Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

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

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1, strong "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, weak "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.

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.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

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

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Creatinine	mg/dl	88.4	μmol/l
Glucose	mg/dl	0.0555	mmol/l

Note: conventional unit × conversion factor = SI unit.

ALBUMINURIA CATEGORIES IN CKD

		ACR (approximate equivalent)		
Category	AER (mg/24 h)	(mg/mmol)	(mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased[a]
A3	>300	>30	>300	Severely increased[b]

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

HbA1c CONVERSION CHART

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	**7.0**	**53**	**8.0**	**64**	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	**6.5**	**48**	**7.5**	**58**	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139

IFCC–HbA1c (mmol/mol) = [DCCT–HbA1c (%) – 2.15] × 10.929.
DCCT, Diabetes Control and Complications Trial; HbA1c, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.
Source: Diabetes UK, www.diabetes.org.uk.

Abbreviations and acronyms

ACEi	angiotensin-converting enzyme inhibitor(s)
ACR	albumin–creatinine ratio
AKI	acute kidney injury
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CKD	chronic kidney disease
CrCl	creatinine clearance
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
ERT	Evidence Review Team
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist(s)
GMI	glucose management index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated hemoglobin
HR	hazard ratio
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	major adverse cardiovascular events
MET	metabolic equivalent
MRA	mineralocorticoid receptor antagonist(s)
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
RAS(i)	renin–angiotensin system (inhibition/inhibitors)
RCT	randomized controlled trial
RR	relative risk
SCr	serum creatinine
SGLT2i	sodium–glucose cotransporter-2 inhibitor(s)
SMBG	self-monitoring of blood glucose
T1D	type 1 diabetes
T2D	type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study Group
US	United States

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in December 2021, and updated in February 2022. It is designed to assist with 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 professionals 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.

Foreword

Kidney International (2022) **102** (Suppl 5S), S1–S127; https://doi.org/10.1016/j.kint.2022.06.008

With the growing awareness that chronic kidney disease (CKD) is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with its stated mission to "improve the care and outcomes of patients with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines."

The prevalence of diabetes around the world has reached epidemic proportions. The International Diabetes Federation estimated that 537 million people were living with diabetes in 2021. This number is expected to increase to 784 million by 2045. It has been estimated that 40% or more of people with diabetes will develop CKD, including a significant number who will develop kidney failure requiring dialysis or transplantation.

With a number of new agents targeting a variety of mechanistic approaches to improving outcomes for people with diabetes and kidney disease, KDIGO published its first Clinical Practice Guideline for Diabetes Management in CKD in 2020. However, in just under 2 years, the development of additional treatments and the continued publication of high-quality trials in patients with diabetes and CKD warranted a reevaluation of the original 2020 guidance to help clinicians and patients appropriately consider these new advances for their practice.

As with the 2020 guideline, this guideline update features a combination of both graded recommendations and practice points. Graded recommendations were based on a systematic review of the evidence and are graded for both strength of the recommendation (level 1, "strong" or level 2, "weak") and quality of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). 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 was not deemed a high priority for systematic review, to help readers implement the guidance from graded recommendation, 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.

Once again, we thank Ian de Boer, MD, MS and Peter Rossing, MD, DMSc for leading this important initiative. We are especially grateful to the continued dedication of the original Work Group members who volunteered their time and expertise to this update. In addition, we thank the independent Evidence Review Team (ERT) from Cochrane Kidney and Transplant led by Jonathan Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Giovanni F.M. Strippoli, MD, MPH, M Med (Clin Epi), PhD, and David Tunnicliffe, PhD who were contracted to update their evidence review, thus informing this latest version of the guideline.

In keeping with KDIGO's policy for transparency and rigorous public review during the guideline development process, the draft guideline was made broadly available for open commenting. The feedback received from the public review has been carefully considered by the Work Group members and the guideline revised, as was deemed appropriate, for its formal release.

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Abstract

The *Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* (CKD) represents a focused update of the KDIGO 2020 guideline on the topic. The guideline targets a broad audience of clinicians treating diabetes and CKD. Topic areas for which recommendations are updated include: Chapter 1: Comprehensive care in patients with diabetes and CKD and Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD. Previous chapters on Glycemic monitoring and targets in patients with diabetes and CKD (Chapter 2), Lifestyle interventions in patients with diabetes and CKD (Chapter 3), and Approaches to management of patients with diabetes and CKD (Chapter 5) have been deemed current and their content has remained unchanged. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and areas of future research are also presented.

Keywords: angiotensin-converting enzyme inhibitor; angiotensin II receptor blocker; chronic kidney disease; dialysis; evidence-based; GLP-1 receptor agonist; glycemia; glycemic monitoring; glycemic targets; guideline; HbA1c; hemodialysis; KDIGO; lifestyle; metformin; models of care; nutrition; renin-angiotensin system; self-management; SGLT2 inhibitor; systematic review; team-based care

CITATION

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Introduction

The KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD) follows only 2 years after the original KDIGO 2020 Clinical Practice Guideline on this topic. The update was motivated by the wealth of high-quality new information that has quickly become available since the original 2020 guideline was published and by calls from the community to help guide application of these new data. The short interval between guidelines reflects the rapid pace of advancement in treatment of diabetes and CKD.

A comprehensive process was undertaken to update the guideline. The Evidence Review Team (ERT) first updated the systematic literature search for each topic covered by the 2020 guideline. The Work Group reviewed the ERT summary of new studies by topic and judged by topic whether there was sufficient new evidence to conduct a full quantitative reassessment with reconsideration of recommendations. Such full reassessments were deemed to be warranted for use of sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and mineralocorticoid receptor antagonists (MRA). For these topics, the ERT updated the detailed extraction and meta-analysis of available data, and the Work Group revised the corresponding guideline chapters accordingly.

Updates to sections on SGLT2i and GLP-1 RA include new data, additional discussion, modification of the SGLT2i recommendation to reflect new evidence of benefits and safety with estimated glomerular filtration rate (eGFR) $\geq$20 ml/min per 1.73 m^2 (from $\geq$30 ml/min per 1.73 m^2 previously) among people with type 2 diabetes (T2D), and revised or added practice points and research recommendations. In addition, the SGLT2i section was moved from the "Glucose-lowering therapies" chapter to the "Comprehensive care" chapter to reflect growing acknowledgment that these drugs are an essential component of CKD care irrespective of glycemic effects. These changes were supported by multiple new large randomized controlled trials assessing the benefits and risks of SGLT2i and GLP-1 RA.

A new section on MRA was added to the chapter on "Comprehensive care in patients with diabetes and CKD" (Chapter 1), with a new recommendation supporting use of nonsteroidal MRA for patients with T2D, residual albuminuria despite first-line treatments for diabetes and CKD, and normal serum potassium concentration. This section and recommendation were indicated largely by 2 new trials evaluating the benefits and risks of finerenone, a novel nonsteroidal MRA (ns-MRA).

The 2022 guideline, as was the 2020 guideline, is designed to apply to a broad population of patients with diabetes and CKD. Type 1 diabetes (T1D) and T2D are both addressed, with differences in approach to management highlighted when appropriate. Pharmacologic management of glycemia is one aspect of care that differs substantially by diabetes type. The guideline includes evidence-based recommendations for pharmacologic glucose-lowering treatment in T2D and CKD but defers pharmacologic glucose-lowering treatment of T1D, based on insulin, to existing guidelines from diabetes organizations. Similarly, the Work Group addressed care for patients with all severities of CKD, patients with a kidney transplant, and patients treated with hemodialysis or peritoneal dialysis. CKD is defined as persistently elevated urine albumin excretion ($\geq$30 mg/g [$\geq$3 mg/mmol]), persistently reduced eGFR ($<$60 ml/min per 1.73 m^2), or both, for greater than 3 months, in accordance with current KDIGO guidelines.

This is an evidence-based guideline that focuses on clinical management questions that can be addressed with high-quality scientific evidence. Specifically, we focused on questions that have been addressed using randomized trials that evaluated clinically relevant outcomes. This guideline is not a textbook. Our approach omits important aspects of clinical care that have become standard practice but are not addressed with randomized trials—for which we refer readers to excellent existing texts and reviews—as well as new treatments that have yet to be sufficiently evaluated for application to clinical care.

Concurrent with developing the 2022 guideline, KDIGO partnered with the American Diabetes Association (ADA) to issue a consensus report on the diagnosis and management of diabetes and CKD. This report demonstrates the broad similarities across evidence-based recommendations from the 2 professional societies and emphasizes high-priority interventions to improve the health of people with diabetes and CKD. In addition, the consensus report addresses aspects of CKD prevention, screening, and diagnosis, which are important clinical topics not explicitly covered in the KDIGO guideline.

Diagnostically, CKD occurring among people with diabetes is usually attributed to diabetes, unless other causes are readily evident. Certainly, cases of CKD occurring among people with diabetes are actually heterogeneous, and some are caused by other processes. More work is needed to develop granular approaches to CKD diagnosis and classification in diabetes and to determine the roles of kidney biopsy and biomarkers in this evaluation. Here, we adopt the current clinical approach of treating most presentations of diabetes and CKD similarly, modifying the approach as appropriate according to albuminuria or eGFR category. We avoid the use of the term "diabetic kidney disease" to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, although this term is entirely appropriate when this limitation is recognized. We also avoid the use of the term "diabetic nephropathy," an outdated term for which there is currently no consensus definition. Prevention, screening, and diagnosis of new-onset diabetes after transplantation are also important topics that were considered to be out of scope for this guideline.

The care of patients with diabetes and CKD is multifaceted and complex, as highlighted in our first chapter, "Comprehensive care in patients with diabetes and CKD." Several critical aspects of this comprehensive care, such as blood

pressure and lipid management, were addressed in other KDIGO guidelines. These topics were not reviewed for the current guideline, and we refer readers to prior KDIGO guidelines and the ADA-KDIGO consensus report. Fortunately, new treatments relevant to people with diabetes and CKD are currently being developed. However, such treatments were not included in this guideline if adequately powered randomized trials with clinical outcomes have not yet been reported.

The Work Group aimed to generate an updated guideline that is both rigorously devoted to existing evidence and clinically useful. The group made recommendations only when they were supported by high-quality evidence from a systematic review generated by the ERT. However, practice points were made when evidence was insufficient to make a recommendation but clinical guidance was thought to be warranted. In some situations, recommendations could be issued for some groups of patients but not others. For example, evidence for patients treated with dialysis was often weak, leading to fewer recommendations for this population.

Fortunately, almost all members of the Work Group, ERT, and KDIGO staff who contributed to the 2020 guideline also agreed to contribute to the 2022 guideline. As Co-Chairs, we would like to recognize the outstanding efforts of all of these dedicated contributors, without whom this guideline would not have been possible. The Work Group was diverse, multinational, multidisciplinary, experienced, thoughtful, and vigilant in its work. Notably, the Work Group included 2 members who have diabetes and CKD who contributed actively as peers to keep the guideline relevant and patient-centered. Incorporating patients as partners has become more common in research, and we are pleased to see that this model is being adopted by additional clinical practice guideline development groups. We hope that the summary guidance provided here will help improve the care of patients with diabetes and CKD worldwide.

Ian H. de Boer, MD, MS
Peter Rossing, MD, DMSc
Diabetes Guideline Co-Chairs

Summary of recommendation statements and practice points

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1. Comprehensive diabetes and CKD management

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).

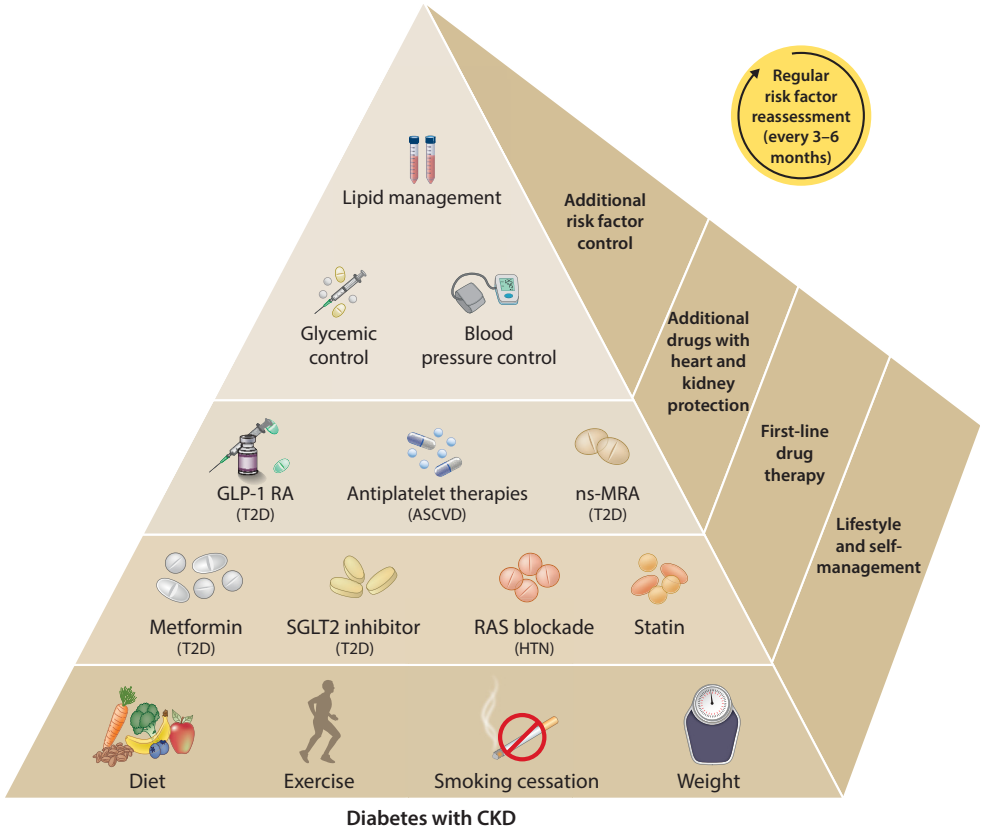


Figure 1 | Kidney–heart risk factor management. People with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive approach to improve kidney and cardiovascular outcomes. This approach should include a foundation of lifestyle modification and self-management for all patients, upon which are layered first-line drug therapies according to clinical characteristics (in parentheses), additional drugs with proven kidney and heart protection as guided by assessments of residual risk, and additional interventions as needed to further control risk factors. Glycemic control is based on insulin for type 1 diabetes (T1D) and a combination of metformin and sodium–glucose cotransporter-2 inhibitors (SGLT2i) for type 2 diabetes (T2D). Metformin may be given when estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2, and SGLT2i should be initiated when eGFR is ≥20 ml/min per 1.73 m^2 and continued as tolerated, until dialysis or transplantation is initiated. Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension (HTN). A statin is recommended for all patients with T1D or T2D and CKD. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are preferred glucose-lowering drugs for people T2D if SGLT2i and metformin are insufficient to meet glycemic targets or if they are unable to use SGLT2i or metformin. A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) can be added to first-line therapy for patients with T2D and high residual risks of kidney disease progression and cardiovascular events, as evidenced by persistent albuminuria (>30 mg/g [>3 mg/mmol]). Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among patients with high risk of atherosclerotic cardiovascular disease (ASCVD).

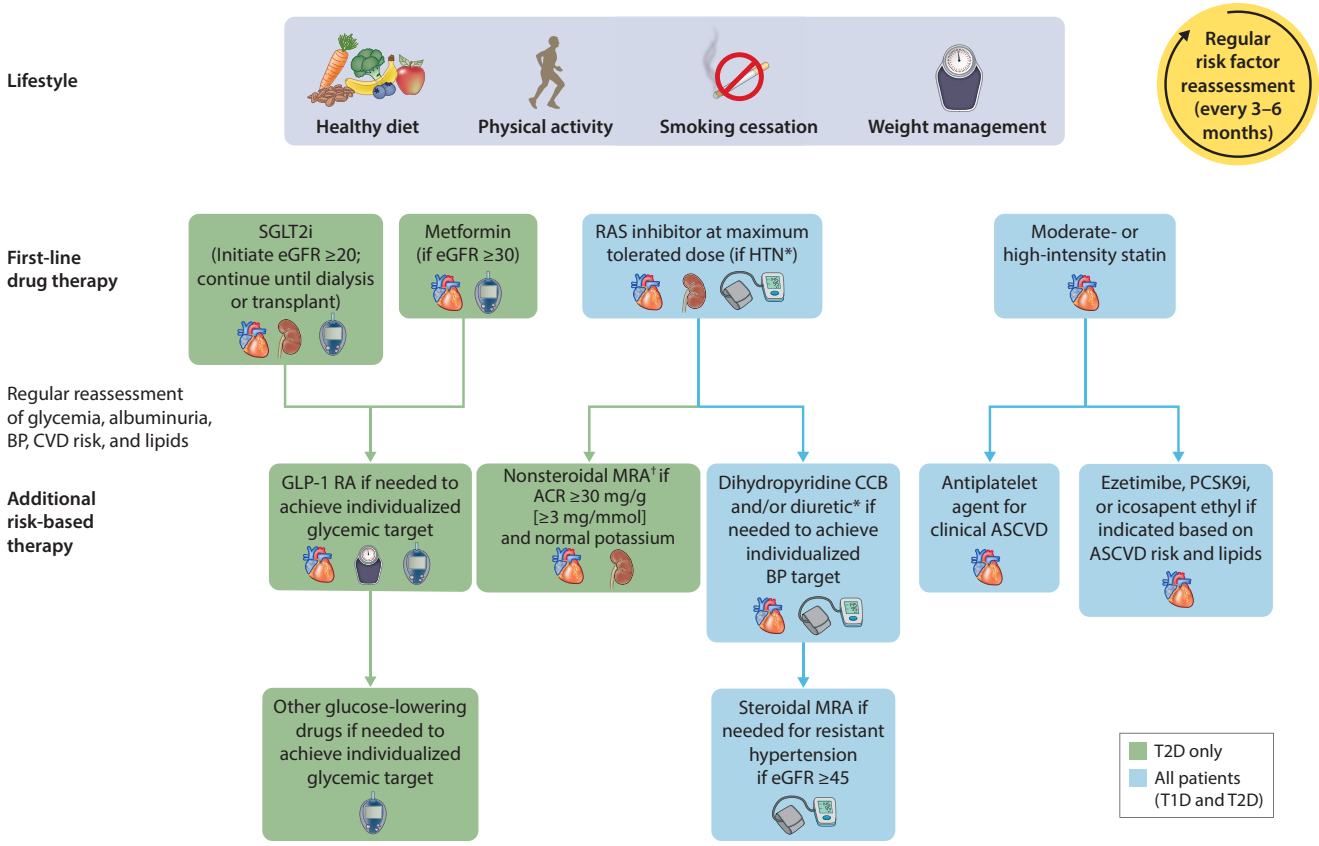


Figure 2 | Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease. *Angiotensin-converting ezyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) should be first-line therapy for hypertension (HTN) when albuminuria is present, otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all 3 classes are often needed to attain blood pressure (BP) targets. †Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist (MRA) with proven clinical kidney and cardiovascular benefits. Icons presented indicate the following benefits: blood pressure cuff = blood pressure–lowering; glucometer = glucose-lowering; heart = heart protection; kidney = kidney protection; scale, weight management; ACR, albumin-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; 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; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

1.2. Renin–angiotensin system (RAS) blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*.

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

Practice Point 1.2.3: 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 (Figure 4).

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping the ACEi or ARB immediately (Figure 4).

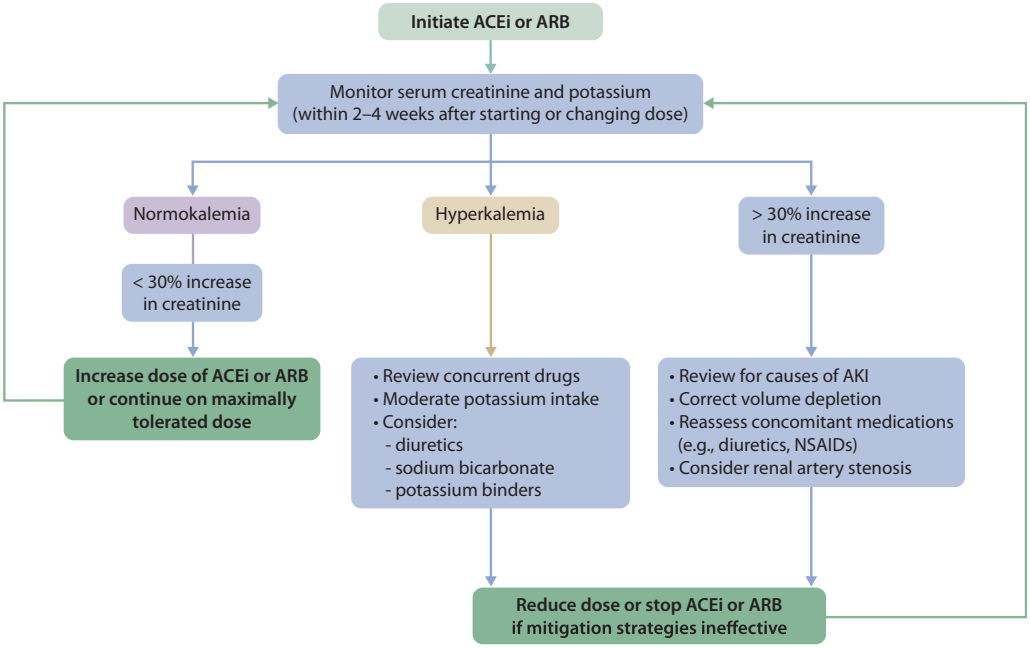


Figure 4 | Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) treatment—dose adjustment and monitoring of side effects. AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug.

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

1.3. Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

Recommendation 1.3.1: 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 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen (Figure 6).

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 1.3.6: 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 kidney replacement therapy is initiated.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

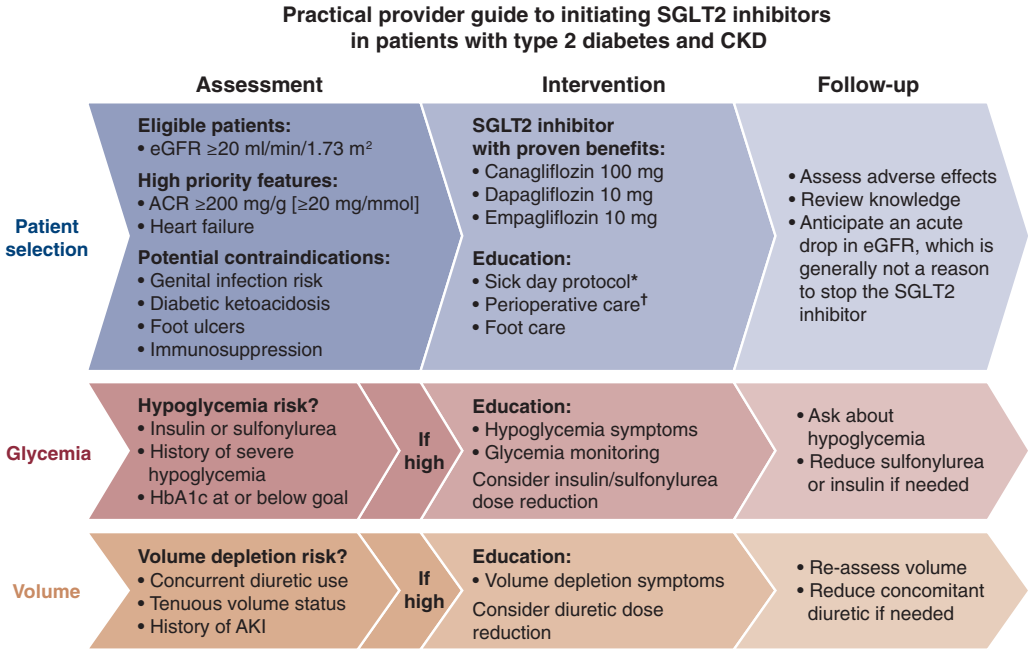


Figure 6 | Practical approach to initiating sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with type 2 diabetes and chronic kidney disease (CKD). *Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold SGLT2i, keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. †Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis; withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required; withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring 1 or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are <1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally. Adapted from Zoungas S, de Boer IH. SGLT2 inhibitors in diabetic kidney disease. *Clin J Am Soc Nephrol*. 2021;16:631–633.[148] Copyright © 2021 by the American Society of Nephrology. ACR, albumin-creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

1.4. Mineralocorticoid receptor antagonists (MRA)

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m², normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

Practice Point 1.4.1: Nonsteroidal MRA are most appropriate for patients 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 1.4.2: A nonsteroidal MRA can be added to a RASi and an SGLT2i for treatment of T2D and CKD.

Practice Point 1.4.3: To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

Practice Point 1.4.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 1.4.5: A steroidal MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

1.5. Smoking cessation

Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products *(1D)*.

Practice Point 1.5.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Chapter 2: Glycemic monitoring and targets in patients with diabetes and CKD

2.1. Glycemic monitoring

Recommendation 2.1.1: We recommend using hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD *(1C)*.

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in glucose-lowering therapy.

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4–G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.

Practice Point 2.1.3: A glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) data can be used to index glycemia for individuals in whom HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms.

Practice Point 2.1.4: Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) may help prevent hypoglycemia and improve glycemic control when glucose-lowering therapies associated with risk of hypoglycemia are used.

Practice Point 2.1.5: For patients with T2D and CKD who choose not to do daily glycemic monitoring by CGM or SMBG, glucose-lowering agents that pose a lower risk of hypoglycemia are preferred and should be administered in doses that are appropriate for the level of eGFR.

Practice Point 2.1.6: CGM devices are rapidly evolving with multiple functionalities (e.g., real-time and intermittently scanned CGM). Newer CGM devices may offer advantages for certain patients, depending on their values, goals, and preferences.

2.2. Glycemic targets

Recommendation 2.2.1: We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 14) *(1C)*.

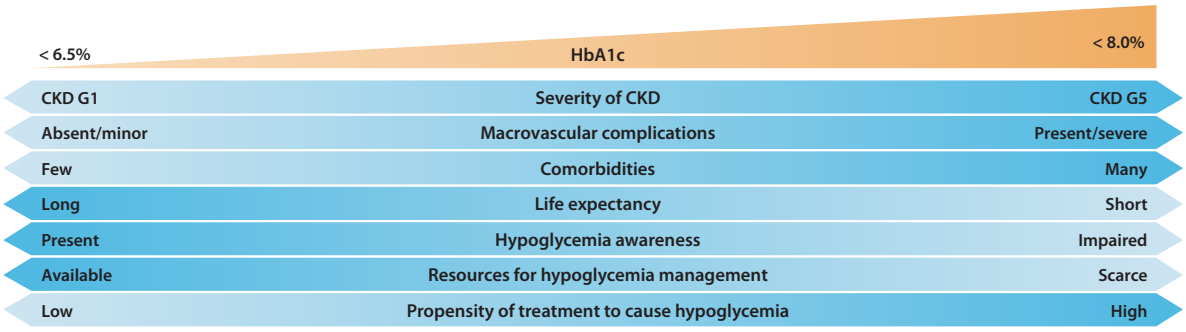


Figure 14| Factors guiding decisions on individual glycated hemoglobin (HbA1c) targets. CKD, chronic kidney disease; G1, estimated glomerular filtration rate (eGFR) ≥90 ml/min per 1.73 m^2; G5, eGFR <15 ml/min per 1.73 m^2.

Practice Point 2.2.1: Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of glucose-lowering agents that are not associated with hypoglycemia.

Practice Point 2.2.2: CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA1c for defining glycemic targets in some patients.

Chapter 3: Lifestyle interventions in patients with diabetes and CKD

3.1. Nutrition intake

Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.

Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis *(2C)*.

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Recommendation 3.1.2: 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 patients with diabetes and CKD *(2C)*.

Practice Point 3.1.3: Shared decision-making should be a cornerstone of patient-centered nutrition management in patients with diabetes and CKD.

Practice Point 3.1.4: Accredited nutrition providers, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the multidisciplinary nutrition care of patients with diabetes and CKD.

Practice Point 3.1.5: Healthcare providers should consider cultural differences, food intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to patients and their families.

3.2. Physical activity

Recommendation 3.2.1: We recommend that patients with diabetes and 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 3.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.

Practice Point 3.2.2: Patients should be advised to avoid sedentary behavior.

Practice Point 3.2.3: For patients 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 3.2.4: Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR ≥30 ml/min per 1.73 m^2.

Chapter 4: Glucose-lowering therapies in patients with T2D and CKD

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with both metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control (Figure 23).

Practice Point 4.2: Most patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i.

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 25).

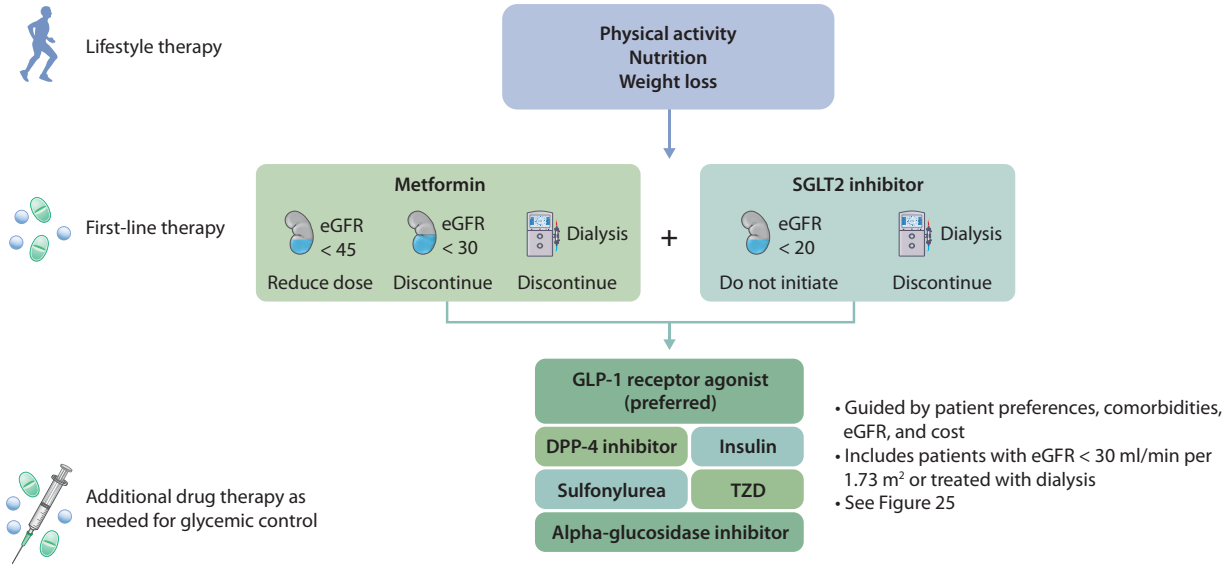


Figure 23 | Treatment algorithm for selecting glucose-lowering drugs for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

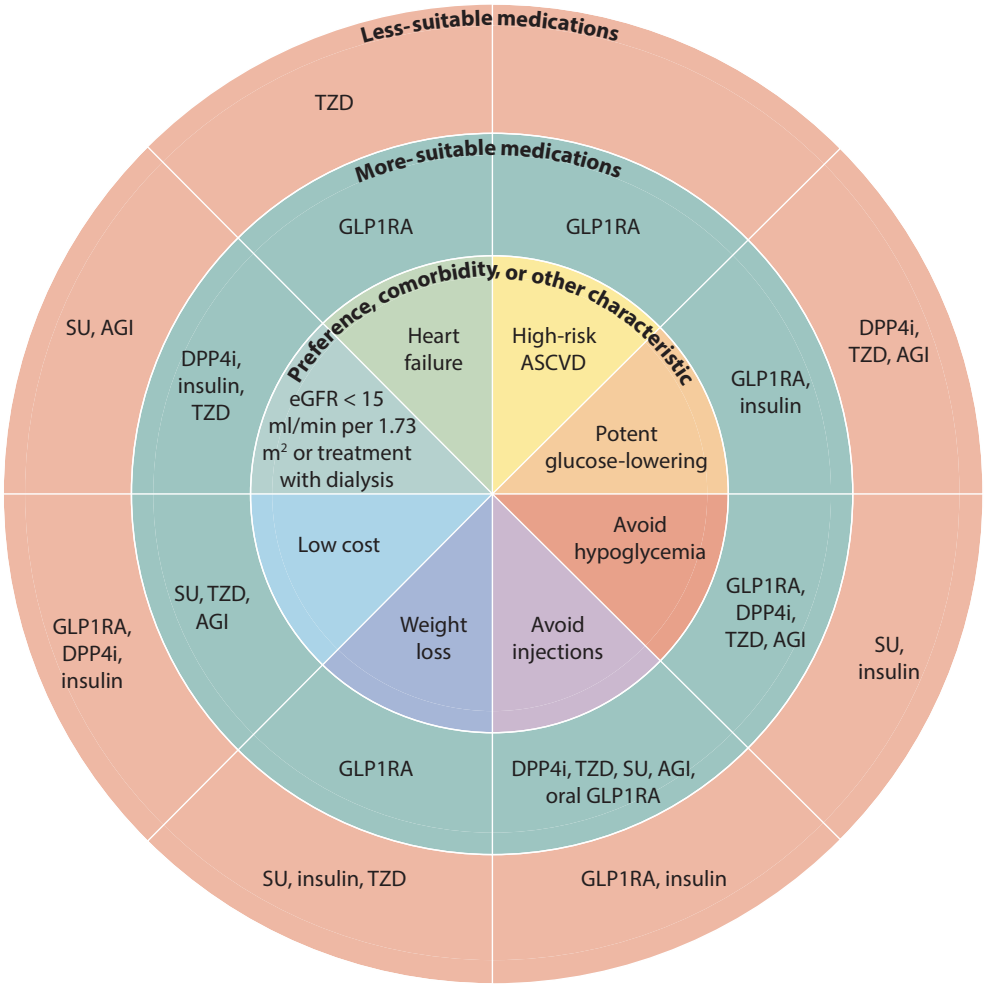


Figure 25 | Patient factors influencing the selection of glucose-lowering drugs other than sodium–glucose cotransporter-2 inhibitor (SGLT2i) and metformin in type 2 diabetes (T2D) and chronic kidney disease (CKD). AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; TZD, thiazolidinedione.

4.1. Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin *(1B)*.

Practice Point 4.1.1: Treat kidney transplant recipients with T2D and an eGFR ≥30 ml/min per 1.73 m^2 with metformin according to recommendations for patients with T2D and CKD.

Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when the eGFR is <60 ml/min per 1.73 m^2 (Figure 27).

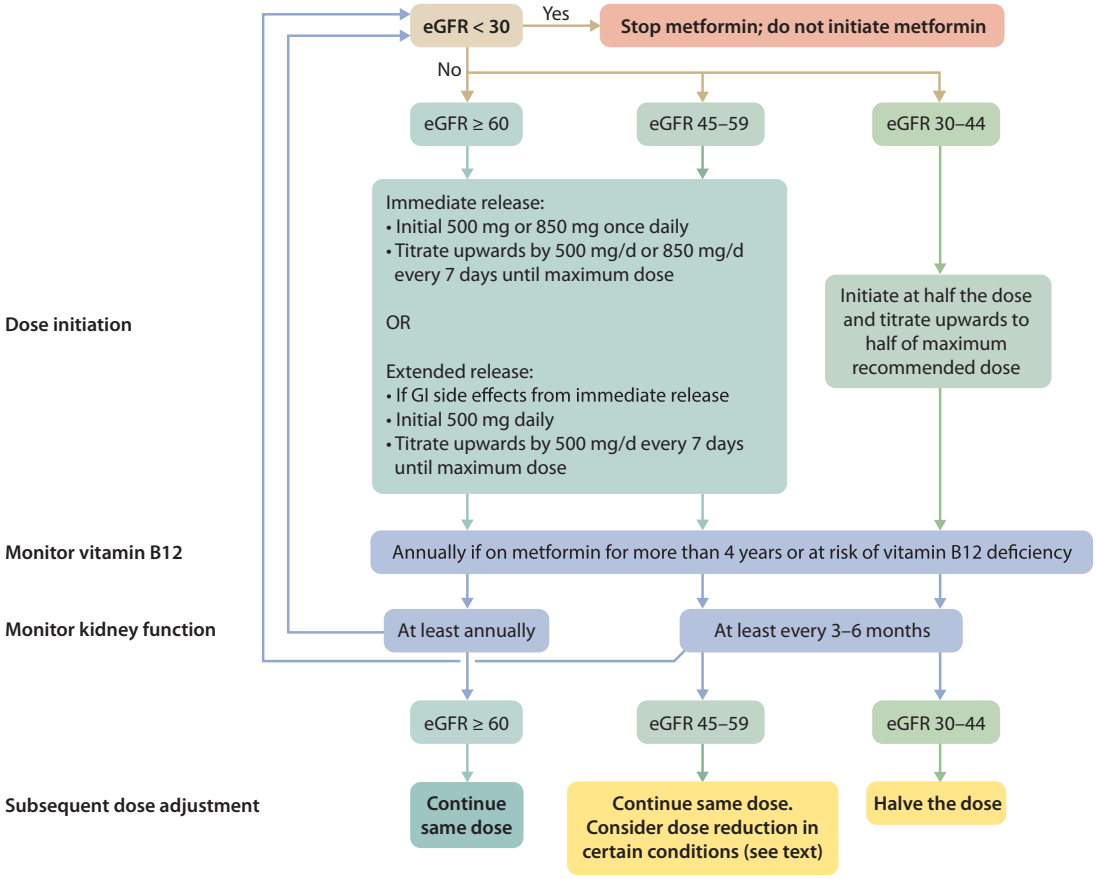


Figure 27 | Suggested approach in dosing metformin based on the level of kidney function. eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); GI, gastrointestinal.

Practice Point 4.1.3: Adjust the dose of metformin when the eGFR is <45 ml/min per 1.73 m^2, and for some patients when the eGFR is 45–59 ml/min per 1.73 m^2 (Figure 27).

Practice Point 4.1.4: Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years.

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

Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 29).

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 μg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 μg and 20 μg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Figure 29 | Dosing for available glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dose modification for chronic kidney disease (CKD). CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate.

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

Practice Point 4.2.5: GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

Chapter 5: Approaches to management of patients with diabetes and CKD

5.1. Self-management education programs

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (Figure 30) (*1C*).

Key objectives are to:

- Improve diabetes-related knowledge, beliefs, and skills
- Improve self-management and self-motivation
- Encourage adoption and maintenance of healthy lifestyles
- Improve vascular risk factors
- Increase engagement with medication, glucose monitoring, and complication screening programs
- Reduce risk to prevent (or better manage) diabetes-related complications
- Improve emotional and mental well-being, treatment satisfaction, and quality of life

Figure 30 | Key objectives of effective diabetes self-management education programs. Reprinted from *The Lancet Diabetes & Endocrinology*, volume 6, Chatterjee S, Davies MJ, Heller S, Speight J, Snoek FJ, Khunti K. Diabetes structured self-management education programmes: a narrative review and current innovations, pages 130–142, Copyright © 2018, with permission from Elsevier.[403]

Practice Point 5.1.1: Healthcare systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.

5.2. Team-based integrated care

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD *(2B)*.

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, healthcare assistants, community workers, and peer supporters) preferably with knowledge of CKD (Figure 35).

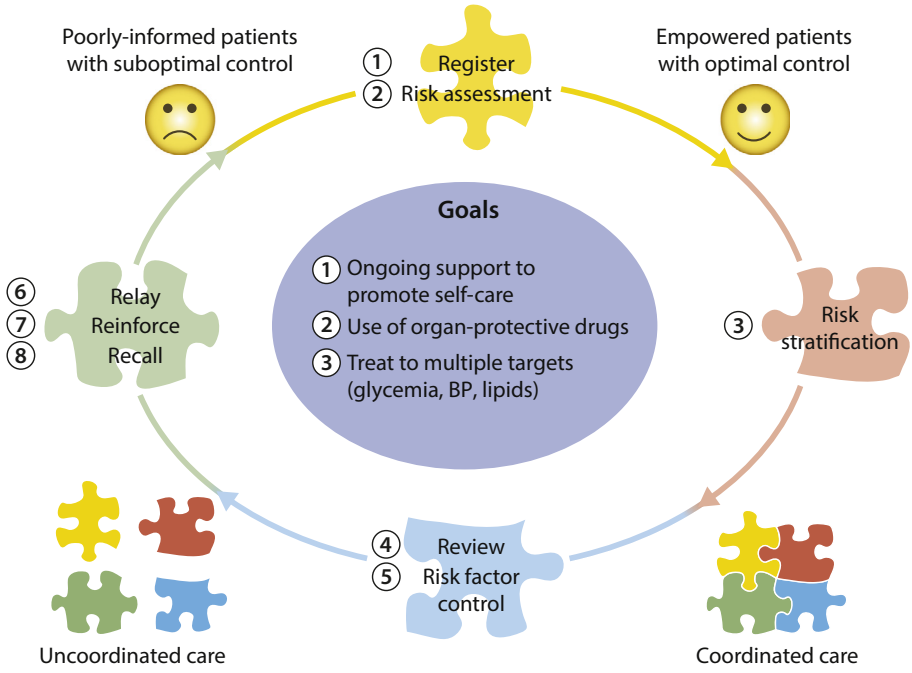


Figure 35 | Team-based integrated care delivered by physicians and nonphysician personnel supported by decision-makers. BP, blood pressure.

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1 Comprehensive diabetes and CKD management

Optimal management of CKD in diabetes is a complex, multidisciplinary, cross-functional team effort. It bridges from diabetes management in general practice or diabetology settings to CKD management in the nephrology setting. Since multi-morbidity is common among people with diabetes and CKD, care usually involves many other specialties, including but not limited to ophthalmology, neurology, orthopedic surgery, and cardiology. With the patient at the center, the team includes medical doctors, nurses, dietitians, pharmacists, social workers, educators, lab technicians, podiatrists, family members, and potentially many others, depending on local organization and structure. In this guideline, the background and organization of this chronic care model are described in Section 5.2: Team-based integrated care.

Structured education is critical to engage people with diabetes and CKD to self-manage their disease and participate in the necessary shared decision-making regarding the management plan. Several models have been proposed, as outlined in Chapter 5. It is essential that education be structured, monitored, individualized, and evaluated in order for it to be effective.

Individuals with diabetes and CKD are at risk for acute diabetes-related complications such as hypoglycemia and diabetic ketoacidosis; long-term complications such as retinopathy, neuropathy, and foot complications; the risk of kidney failure with a need for dialysis or transplantation; and in particular, the risk of cardiovascular complications, including myocardial infarction, ischemia, arrhythmia, and heart failure. Comprehensive diabetes care, therefore, includes regular screening for these complications and management of the many cardiovascular risk factors in addition to hyperglycemia, such as hypertension, dyslipidemia, obesity, and lifestyle factors, including diet, smoking, and physical activity.

Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease (CVD),[1] with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention as per clinical guidelines.[2] Aspirin may be considered for primary prevention among high-risk individuals,[1] but it should be balanced against an increased risk for bleeding, including thrombocytopathy with low glomerular filtration rate (GFR).[3] Although the risk for thrombotic and embolic events is high, the optimal antiplatelet and antithrombotic therapy in diabetes and CKD has not been well studied.[4]

For CVD prevention, statin therapy generally should also be used for secondary prevention among those with established CVD, for primary prevention for individuals over age 40 with diabetes, and in primary prevention for persons over age 40 with CKD stages 1–4 and kidney transplant.[5] However, there does not appear to be a benefit in persons on chronic dialysis, likely due to competing risk. Specific details on lipid management are covered in other KDIGO guidelines.

Among persons with type 2 diabetes (T2D), cardiovascular risk and mortality are dependent on the number of uncontrolled risk factors.[6] Multifactorial intervention is needed to target these risk factors with lifestyle modification, including smoking cessation support, dietary counseling, physical activity, and pharmacologic intervention. Multifactorial intervention in T2D reduced the onset and progression of diabetic kidney disease, compared to currently recommended care.[7] In addition, studies in people with T2D and early CKD demonstrated the long-term benefit of multifactorial intervention on the development of microvascular and macrovascular complications and mortality.[8,9] We have seen reduction in progression of CKD in T2D with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blocker (ARB), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and nonsteroidal mineralocorticoid receptor antagonists (MRA), as discussed in subsequent sections, as well as with endothelin receptor antagonists. Ongoing trials may offer additional new opportunities.[10]

With multiple effective treatment options now often available to patients, initiation and titration of comprehensive care becomes more complicated. Sequencing of interventions should be individualized to each patient's pressing individual clinical needs. For glycemic management in T2D, most guidelines recommend starting with metformin, while others suggest starting with SGLT2i or glucagon-like peptide-1 receptor agonists (GLP-1 RA) in patients with CKD or atherosclerotic cardiovascular disease (ASCVD), as their kidney and heart protective effects are better documented. This guideline recommends that metformin and an SGLT2i generally both be used as first-line treatment of patients with T2D and CKD, when eGFR allows (Figures 1 and 2). In addition, many drugs have hemodynamic effects to reduce intraglomerular pressure, including renin-angiotensin system inhibitors (RASi), SGLT2i, and MRA. It is logical to institute and titrate these sequentially, especially for patients with high

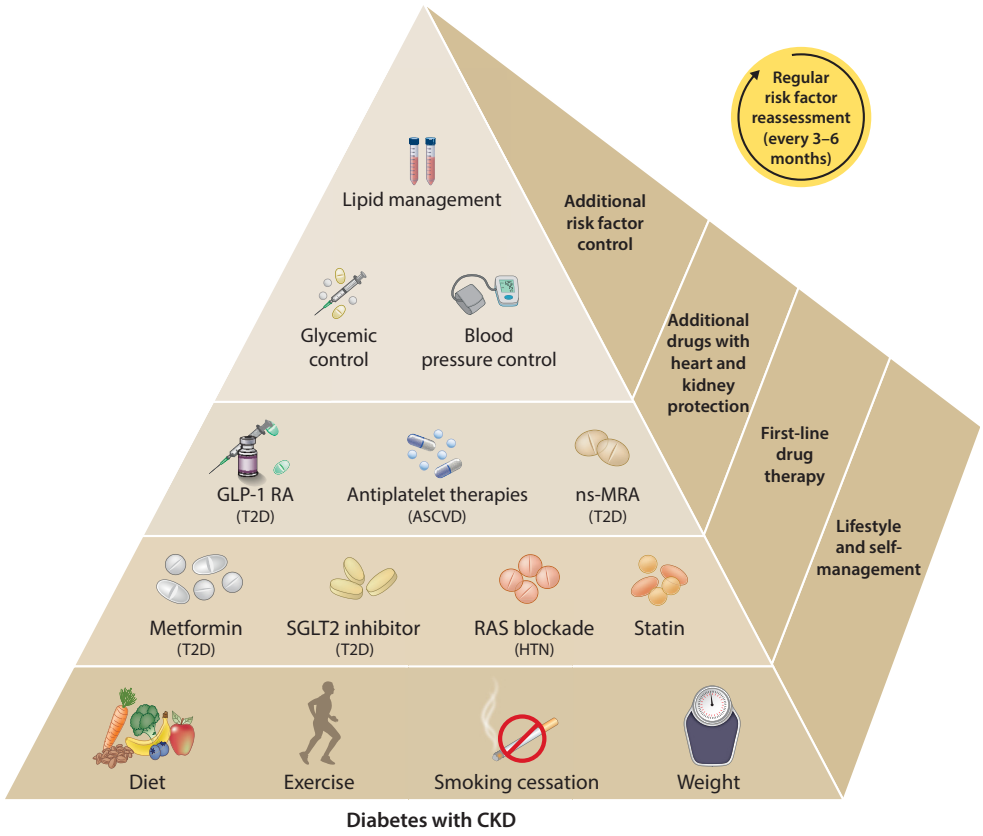


Figure 1 | Kidney–heart risk factor management. People with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive approach to improve kidney and cardiovascular outcomes. This approach should include a foundation of lifestyle modification and self-management for all patients, upon which are layered first-line drug therapies according to clinical characteristics (in parentheses), additional drugs with proven kidney and heart protection as guided by assessments of residual risk, and additional interventions as needed to further control risk factors. Glycemic control is based on insulin for type 1 diabetes (T1D) and a combination of metformin and sodium–glucose cotransporter-2 inhibitors (SGLT2i) for type 2 diabetes (T2D). Metformin may be given when estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2, and SGLT2i should be initiated when eGFR is ≥20 ml/min per 1.73 m^2 and continued as tolerated, until dialysis or transplantation is initiated. Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension (HTN). A statin is recommended for all patients with T1D or T2D and CKD. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are preferred glucose-lowering drugs for people T2D if SGLT2i and metformin are insufficient to meet glycemic targets or if they are unable to use SGLT2i or metformin. A nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) can be added to first-line therapy for patients with T2D and high residual risks of kidney disease progression and cardiovascular events, as evidenced by persistent albuminuria (>30 mg/g [>3 mg/mmol]). Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among patients with high risk of atherosclerotic cardiovascular disease (ASCVD).

risk of acute kidney injury due to low eGFR or concurrent use of medications that may contribute to kidney hypoperfusion, such as diuretics. If and when sequencing of treatments is required, it is critically important to ensure that all effective and indicated treatments are implemented in an expeditious manner to maximize benefits. To accomplish this, frequent contacts may be needed and multidisciplinary team care can be essential, as outlined in Section 5.2.

This guideline focuses on selected topics for which evidence-based guidance can be provided; it does not cover topics like blood pressure and lipid management as these are dealt with in other KDIGO guidelines. However, management of CKD in diabetes requires multifactorial risk factor control, including targeting all of the risk factors mentioned above and also those indicated in Figures 1 and 2.

Overall, the guideline is designed to apply to a broad population of patients with diabetes and CKD. T1D and T2D are both addressed, with differences in approach to management highlighted as appropriate. Pharmacologic management of glycemia is one aspect of care that differs substantially by diabetes type; the benefits of nonsteroidal MRA have been demonstrated only in T2D with CKD. The GLP-1 RA are also recommended only in the T2D population. The benefits of SGLT2i have been demonstrated in persons with CKD with or without diabetes. SGLT2i have not been studied in outcome trials of patients with T1D; however, studies have shown some promise, but also some risk, in this population. There is a substantial difference in the evidence base; thus, this guideline includes evidence-based recommendations for pharmacologic glucose-lowering treatment in T2D and CKD. However, this guideline defers pharmacologic glucose-lowering treatment of T1D, based on insulin, to existing guidelines from diabetes organizations. Similarly, the Work Group addressed care for patients with all severities of CKD, patients with a kidney

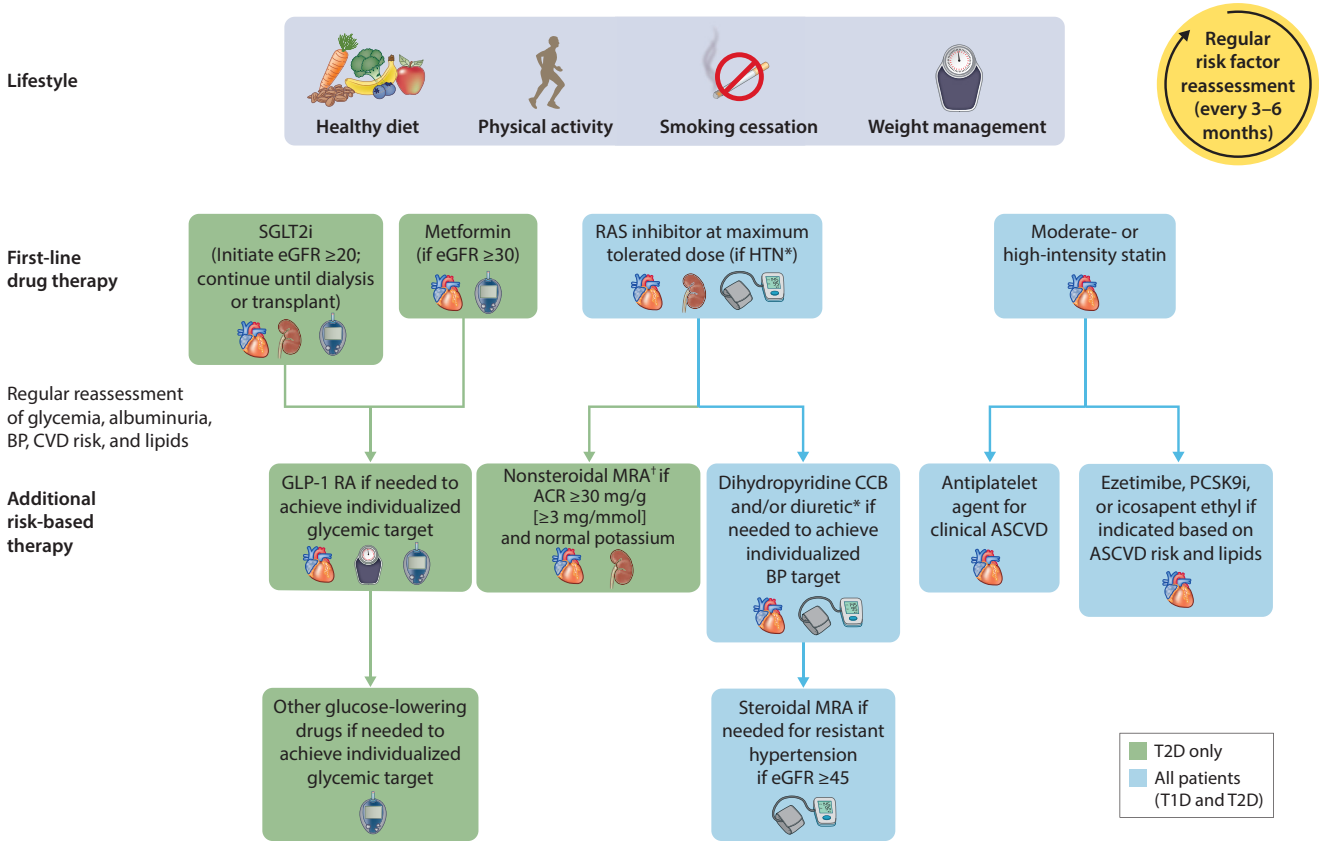


Figure 2 | Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease. *Angiotensin-converting ezyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) should be first-line therapy for hypertension (HTN) when albuminuria is present, otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all 3 classes are often needed to attain blood pressure (BP) targets. †Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist (MRA) with proven clinical kidney and cardiovascular benefits. Icons presented indicate the following benefits: blood pressure cuff = blood pressure–lowering; glucometer = glucose-lowering; heart = heart protection; kidney = kidney protection; scale, weight management; ACR, albumin-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; 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; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

transplant, and patients treated with hemodialysis or peritoneal dialysis. CKD is defined as persistently elevated urine albumin excretion (≥30 mg/g [≥3 mg/mmol]), persistently reduced eGFR (eGFR <60 ml/min per 1.73 m^2), or both, for more than 3 months, in accordance with current KDIGO guidelines.

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).

As kidney function deteriorates and reaches lower GFR, changes to types and doses of medications often need to be adjusted. In addition, management of anemia, bone and mineral disorders, fluid and electrolyte disturbances, and eventually dialysis and transplantation become increasingly dominant. As other KDIGO guidelines cover these latter topics, they are not addressed in the current guideline. However, to the extent possible, guidance is provided in relation to the selected topics, particularly diabetes monitoring, glycemia management, and RAS blockade, as well as lifestyle factors for all CKD severities.

Research recommendations

- Additional trials to prevent CKD progression and CVD are needed. These studies would address how best to combine lifestyle factors and the multiple new therapies (such as SGLT2i and MRA) compared to standard of care
- Studies are needed to examine how best to initiate, combine, and titrate the different treatment options that are part of the comprehensive care.
- The benefit of new therapies and multifactorial intervention should be tested in broader populations with CKD and diabetes including T1D, dialysis, and kidney transplant treated patients.
- Studies should be initiated to evaluate the concept of precision medicine in diabetes and CKD. Should all patients receive the same management/treatment approach to comprehensive care, or should it be tailored based on the individual CKD/diabetes type and risk profile?

- Implementation science research should evaluate ways to improve dissemination and implementation of evidence-based therapies.

1.2 Renin-angiotensin system (RAS) blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*.

This recommendation places a high value on the potential benefits of RAS blockade with ACEi or ARBs for slowing the progression of CKD in patients with diabetes, while it places a relatively lower value on the side effects of these drugs and the need to monitor kidney function and serum potassium. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. Moderately or severely increased albuminuria is related to increased kidney and cardiovascular risk compared to normal albumin excretion. The Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria 2 (IRMA-2)[11] and The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION)[12] studies were placebo-controlled trials enrolling patients with T2D and moderately increased albuminuria (30–300 mg/g [3–30 mg/mmol]). They were designed to determine whether RAS blockade reduced the risk of progression and CKD in diabetes, defined as the development of severely increased albuminuria (>300 mg/g [>30 mg/mmol]). The IRMA-2 study showed that treatment with irbesartan, an ARB, was associated with a dose-dependent reduction in the risk of progression of CKD, with an almost 3-fold risk reduction with the highest dose (300 mg per day) at 2 years of follow-up.[11] This effect was independent of the blood pressure–lowering properties of irbesartan. In the INNOVATION trial, the ARB telmisartan was associated with a lower transition rate to overt nephropathy than placebo after 1 year of follow-up.[12] In this trial, telmisartan also significantly reduced blood pressure levels. However, after adjustment for the difference in blood pressure levels between the placebo and treatment groups, the beneficial effect of telmisartan in delaying progression to overt nephropathy persisted.

Furthermore, the beneficial effects of RAS blockade were shown to extend to patients with severely increased albuminuria. Two landmark trials, the Irbesartan Diabetic Nephropathy (IDNT)[13] and the Reduction of Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL)[14] studies, were conducted in patients with T2D and CKD, having albuminuria greater than 1 g/d. In the IDNT trial, treatment with irbesartan compared with placebo resulted in a 33% decrease in the risk of doubling of serum creatinine concentration and was associated with a nonsignificant reduction in the incidence of kidney failure, which was independent of blood pressure. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, kidney failure, and death, each by 16% compared with placebo, in combination with "conventional" antihypertensive treatment. The kidney protective effect conferred by losartan also exceeded the effect attributable to the small differences in blood pressure between the treatment groups.

Consequently, an update to a Cochrane systematic review[15] performed by the Evidence Review Team (ERT) concurred with the original findings that the use of ACEi or ARB treatment in patients with diabetes and CKD was associated with a reduction in the progression of CKD with regard to the development of severely increased albuminuria (relative risk [RR]: 0.45; 95% confidence interval [CI]: 0.29–0.69 and RR: 0.45; 95% CI: 0.35–0.57, respectively) or doubling of serum creatinine (RR: 0.68; 95% CI: 0.47–1.00 and RR: 0.84; 95% CI: 0.72–0.98, respectively) (Supplementary Tables S4[11,12,16–48] and S5[13,34,40,49–53])

ACEi and ARBs are generally well-tolerated. The systematic reviews performed suggested that ACEi and ARB treatment may cause little or no difference in the occurrence of serious adverse events. However, angioedema has been associated with the use of ACEi, with a weighted incidence of 0.30% (95% CI: 0.28–0.32) reported in 1 systematic review.[54] Dry cough is also a known adverse effect of ACEi treatment. It has been postulated that angioedema and cough are due to the inhibition of ACE-dependent degradation of bradykinin, and consideration can be given to switching affected patients to an ARB, with which the incidence of angioedema is not significantly different from that of placebo (ARB: 0.11%; 95% CI: 0.09–0.13 vs. placebo: 0.07%; 95% CI: 0.05–0.09).

Similar dose dependency of the albuminuria-lowering effect, as described for IRMA-2, has been demonstrated in several studies with ACEi and ARB treatments, but the side effects increase with increasing doses. Thus, initiation should begin at a low dose with up-titration to the highest approved dose the patient can tolerate. *Post hoc* analyses of randomized trials and observational cohorts have demonstrated that an initial larger albuminuria reduction is associated with better long-term outcomes.[55,56]

Quality of evidence. The overall quality of the evidence was rated as moderate. From randomized controlled trials (RCTs) that compared an ACEi with placebo/standard, the quality of the evidence for critical outcomes, such as all-cause mortality, moderately increased to severely increased albuminuria progression, and doubling of serum creatinine, was moderate (Supplementary Table S4). Additionally, in RCTs that compared ARB with placebo/standard of care, the quality of the evidence was moderate for these critical outcomes (Supplementary Table S5). In both comparisons, the quality of the evidence was initially downgraded to moderate because

of serious study limitations, with unclear allocation concealment across the studies. Other outcomes, such as cardiovascular mortality, cardiovascular events, and serious adverse events, were sparingly reported in these studies. The imprecision, in addition to study limitations, downgraded the quality of the evidence for these outcomes to low. The overall quality of the evidence has been driven by the critical outcomes of the doubling of serum creatinine and albuminuria progression, and not by the cardiovascular outcomes or adverse events, because of the lack of reporting of these outcomes in trials.

Values and preferences. The progression of CKD to kidney failure, the avoidance or delay in initiating dialysis therapy, and the antecedent risks associated with dialysis were judged to be critically important to patients. In addition, the side effects with ACEi or ARB therapy, and the need for monitoring of blood pressure, serum creatinine, and potassium, were judged to be important and acceptable to the majority of patients. The Work Group, therefore, judged that most, if not all, patients would choose to receive RAS blockade treatment with either an ACEi or ARB for kidney protection effects, compared to receiving no treatment. This recommendation applies to patients with either T1D and T2D, as well as kidney transplant recipients; however, this recommendation does not apply to patients on dialysis.

The evidence does not demonstrate superior efficacy of ACEi over ARB treatment or vice versa, and the choice between these 2 drug classes will depend on other factors, including patient preferences, cost, availability of generic formulations, and side-effects profiles of individual drugs. ACEi-induced cough is the predominant symptom of intolerance to this class of drug, affecting about 10% of patients.[57] In clinical practice, affected patients are often switched to an ARB so as not to lose the kidney protective effects of RAS blockade, although the improvement in tolerability has not been evaluated in an RCT.

Resource use and costs. Generic formulations of both ACEi and ARBs are widely available at low cost in many parts of the world. Moreover, both have been included in the World Health Organization (WHO) list of essential medicines.[58]

Considerations for implementation. ACEi and ARBs are potent medications and can cause hypotension, hyperkalemia, and a rise in serum creatinine. The inhibition of aldosterone action and its effect on efferent arteriole dilatation could result in hyperkalemia and a rise in serum creatinine in patients with renal artery stenosis. Consequently, blood pressure, serum potassium, and serum creatinine should be monitored in patients who are started on RAS blockade or whenever there is a change in the dose of the drug. The changes in blood pressure, potassium, and kidney function are usually reversible if medication is stopped or doses are reduced.

Figure 3 outlines the common types of ACEi and ARBs available and the respective recommended starting and maximum doses based on their blood pressure–lowering effects, including the need for dose adjustment with decline in kidney function. This is only a suggested guide, and formulations and doses may differ among different regulatory authorities.

The use of ACEi and ARB treatment has been associated with an increased risk of adverse effects to the fetus during pregnancy. Women who are planning for pregnancy or who are pregnant while on RAS blockade treatment should have the drug discontinued (see Practice Point 1.2.4).

Rationale

The presence of albuminuria is associated with an increased risk of progression of CKD and the development of kidney failure in patients with CKD and diabetes. It has also been demonstrated that the degree of albuminuria correlates with the risks for kidney failure and that both ACEi and ARBs are effective in the reduction of albuminuria and even reversal of moderately increased albuminuria. It has been documented that the albuminuria-lowering effect is dose-related (but has side effects as well). Thus, for maximal effect, start at a low dose and then up-titrate to the highest tolerated and recommended dose. Notwithstanding their anti-albuminuric effects, improvement in kidney outcomes has been demonstrated in multiple RCTs. In addition, both drugs are well-tolerated, and the benefits of treatment outweigh the inconvenience of needing to monitor kidney function and serum potassium level after initiation or change in the dose of the drug. This recommendation, therefore, places a high value on the moderate-quality evidence demonstrating that RAS blockade with ACEi or ARBs slows the rate of kidney function loss in patients with CKD and diabetes. It places a relatively lower value on the side effects of these drugs and the need to monitor kidney function and serum potassium level.

This is a strong recommendation, as the Work Group judged that the retardation of CKD progression and prevention of kidney failure would be critically important to patients, and the majority of, if not all, suitable patients would be willing to start treatment with an ACEi or ARB. The Work Group also judged that a large majority of physicians would be comfortable initiating RAS blockade treatment and titrating it to the maximum approved or tolerated dose because of its benefits in kidney protection, their familiarity with this drug, and its good safety profile.

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

The benefits of RAS blockade have been less studied in patients with diabetes and CKD without hypertension. Although the IDNT[13] and IRMA-2[11] studies recruited exclusively patients with T2D and hypertension, a small percentage (3.5%) of patients in the RENAAL trial, and 30.9% (163 of 527) of randomized patients in the INNOVATION study were normotensive, suggesting that use of RAS blockade may be beneficial in patients without hypertension.[12,14] Moreover, due to the strong correlation between the severity of albuminuria and the risk of kidney failure in this

Drug		Starting dose	Maximum daily dose	Kidney impairment
ACE inhibitors	Benazepril	10 mg once daily	80 mg	CrCl ≥30 ml/min: No dosage adjustment needed. CrCl <30 ml/min: Reduce initial dose to 5 mg PO once daily for adults. Parent compound not removed by hemodialysis
	Captopril	12.5 mg to 25 mg 2 to 3 times daily	Usually 50 mg 3 times daily (may go up to 450 mg/day)	Half-life is increased in patients with kidney impairment CrCl 10–50 ml/min: administer 75% of normal dose every 12–18 hours. CrCl <10 ml/min: administer 50% of normal dose every 24 hours. Hemodialysis: administer after dialysis. About 40% of drug is removed by hemodialysis
	Enalapril	5 mg once daily	40 mg	CrCl ≤30 ml/min: In adult patients, reduce initial dose to 2.5 mg PO once daily. 2.5 mg PO after hemodialysis on dialysis days; dosage on non-dialysis days should be adjusted based on clinical response
	Fosinopril	10 mg once daily	80 mg	No dosage adjustment necessary Poorly removed by hemodialysis
	Lisinopril	10 mg once daily	40 mg	CrCl 10–30 ml/min: Reduce initial recommended dose by 50% for adults. Max: 40 mg/day CrCl <10 ml/min: Reduce initial dosage to 2.5 mg PO once daily. Max: 40 mg/day
	Perindopril	2 mg once daily	8 mg	Use is not recommended when CrCl <30 ml/min Perindopril and its metabolites are removed by hemodialysis
	Quinapril	10 mg once daily	80 mg	CrCl 61–89 ml/min: start at 10 mg once daily. CrCl 30–60 ml/min: start at 5 mg once daily. CrCl 10–29 ml/min: start at 2.5 mg once daily. CrCl <10 ml/min: insufficient data for dosage recommendation
	Ramipril	2.5 mg once daily	20 mg	Administer 25% of normal dose when CrCl <40 ml/min Minimally removed by hemodialysis
	Trandolapril	1 mg once daily	4 mg	CrCl <30 ml/min: reduce initial dose to 0.5 mg/day
Angiotensin receptor blockers	Azilsartan	20–80 mg once daily	80 mg	Dose adjustment is not required in patients with mild-to-severe kidney impairment or kidney failure
	Candesartan	16 mg once daily	32 mg	In patients with CrCl <30 ml/min, AUC and Cmax were approximately doubled with repeated dosing. Not removed by hemodialysis
	Irbesartan	150 mg once daily	300 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Losartan	50 mg once daily	100 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Olmesartan	20 mg once daily	40 mg	AUC is increased 3-fold in patients with CrCl <20 ml/min. No initial dosage adjustment is recommended for patients with moderate to marked kidney impairment (CrCl <40 ml/min). Has not been studied in dialysis patients
	Telmisartan	40 mg once daily	80 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Valsartan	80 mg once daily	320 mg	No dosage adjustment available for CrCl <30 ml/min – to use with caution. Not removed significantly by hemodialysis

Figure 3 | Different formulations of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs). Dosage recommendations are obtained from the Physician Desk Reference and/or the US Food and Drug Administration, which are based on information from package inserts registered in the US. *Dosage recommendations may differ across countries and regulatory authorities*. AUC, area under the curve; Cmax, maximum or peak concentration; CrCl, creatinine clearance; GFR, glomerular filtration rate; PO, oral.

population, and given that RAS blockade reduces the severity of albuminuria, the Work Group judged that ACEi and ARB treatment may be beneficial in patients with diabetes and albuminuria but without hypertension. Available data suggest that ACEi and ARB treatments are not beneficial for patients with neither albuminuria nor elevated blood pressure. In T1D with neither albuminuria nor elevated blood pressure, neither an ACEi nor an ARB either slowed the progression of histologic features of diabetes and CKD or reduced the incidence of albuminuria over 5 years.[39] In T2D with neither albuminuria nor elevated blood pressure (normal or well-treated), moderately increased albuminuria was observed less frequently with an ARB, but cardiovascular events were increased.[59] A review found 6 studies in normoalbuminuric T2D patients showing benefit on albuminuria progression by RAS blockade, but most patients had hypertension.[60]

Patients with diabetes and hypertension are at lower risk of CKD progression when urine albumin excretion is normal (<30 mg/g [<3 mg/mmol]), and existing evidence does not demonstrate clear clinical benefit of RAS inhibition for CKD progression in this population. Cardiovascular risk reduction is the most important goal of blood pressure management with normal urine albumin excretion, and multiple classes of antihypertensive agents (including RAS inhibitors, diuretics, and dihydropyridine calcium channel blockers) are appropriate in this setting.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

ACEi and ARBs are potent antihypertensive agents that counteract the vasoconstrictive effects of angiotensin II. Moreover, blocking the action of angiotensin II causes selectively greater vasodilatation of the efferent arterioles of the glomeruli, resulting in a decline of the intraglomerular pressure, and not unexpectedly, a decrease in the GFR and a rise in serum creatinine. In addition, RAS blockade inhibits the action of aldosterone, leading to a greater propensity for hyperkalemia. An increase in serum creatinine, if it occurs, will typically happen during the first 2 weeks of treatment initiation, and it should stabilize within 2–4 weeks in the setting of normal sodium and fluid intake.[61] Therefore, patients should be monitored for symptomatic hypotension, hyperkalemia, and excessive rise in serum creatinine within 2–4 weeks after initiating or making a change in the dose of the drug, depending on resource availability and patient preferences. Earlier laboratory monitoring (e.g., within 1 week) may be indicated for patients at high risk of hyperkalemia due to low eGFR, history of hyperkalemia, or borderline high serum potassium concentration. Conversely, a longer time period for laboratory monitoring (e.g., after initiation but not dose titration) may be considered for patients at low risk of hyperkalemia (e.g., patients with normal eGFR and serum potassium level).

Practice Point 1.2.3: 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 (Figure 4).

The rise in serum creatinine should not be a deterrent in using ACEi or ARB therapy in patients with diabetes and

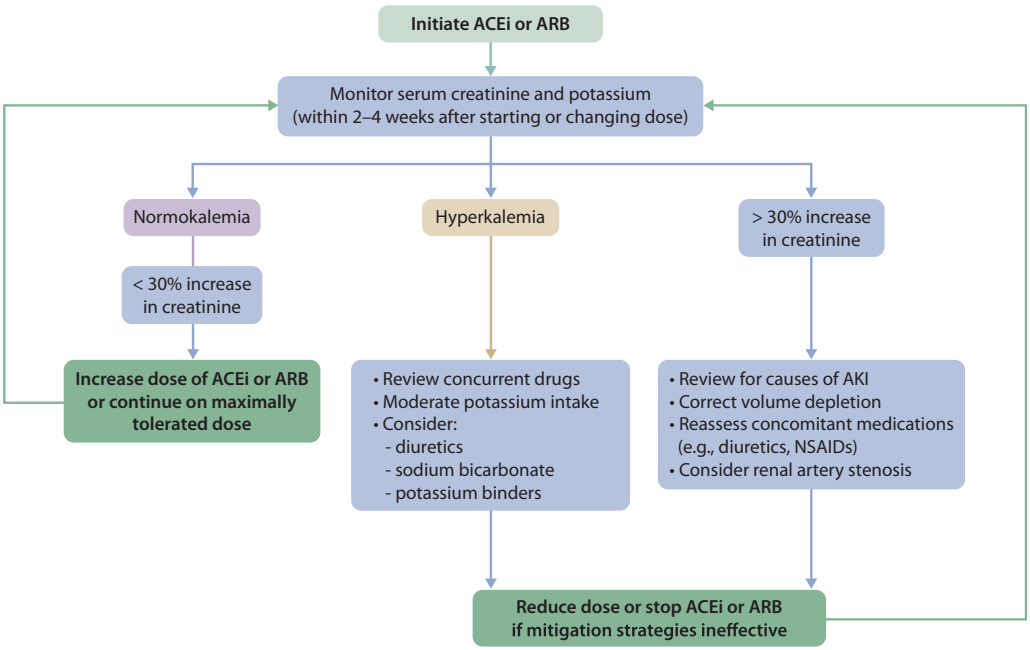


Figure 4 | Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) treatment—dose adjustment and monitoring of side effects. AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug.

CKD, including those with pre-existing kidney disease.[37] Moreover, there were suggestions in clinical trials that the greatest slowing of kidney disease progression occurred in patients with the lowest eGFR at study initiation.[33,62] A review of 12 RCTs that evaluated kidney disease progression among patients with pre-existing kidney disease demonstrated a strong association between acute increases of serum creatinine of up to 30% from baseline that stabilized within 2 months of ACEi therapy initiation and long-term preservation of kidney function.[61]

The most common cause of an acute rise in serum creatinine following the use of a RAS blockade agent results from a decreased effective arterial blood volume, which often occurs in the setting of volume depletion with aggressive diuretic use and low cardiac output seen in heart failure, or with the use of nonsteroidal anti-inflammatory drugs.[63] In addition, bilateral renal artery stenosis (or stenosis of a single renal artery for patients with a single functioning kidney, including kidney transplant recipients) might also be a cause of elevated serum creatinine following initiation of RAS blockade treatment, especially in patients with extensive ASCVD or who are smokers.[61] Therefore, in patients with an acute excessive rise in serum creatinine (>30%), the clinician should evaluate the potential contributing factors highlighted above, sometimes including imaging for bilateral renal artery stenosis aiming to continue ACEi or ARB treatment after these risk factors have been managed.

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

The use of drugs that block the RAS is associated with adverse fetal and neonatal effects, especially with exposure during the second and third trimester. The association with exposure during the first trimester, however, is less consistent.

A systematic review of 72 published case reports and case series that included 186 cases of intrauterine exposure to RAS blockade agents found that 48% of newborns exposed to an ACEi, and 87% of those exposed to an ARB, developed complications,[64] with long-term outcomes occurring in 50% of the exposed children. Across exposure to both ACEi and ARBs, the prevalence of neonatal complications was greater with exposure during the second and third trimesters of pregnancy. The most common complications are related to impaired fetal or neonatal kidney function resulting in oligohydramnios during pregnancy and kidney failure after delivery.[65,66] Other problems include pulmonary hypoplasia, respiratory distress syndrome, persistent patent ductus arteriosus, hypocalvaria, limb defects, cerebral complications, fetal growth restrictions, and miscarriages or perinatal death.[64]

The data regarding first-trimester exposure and the association with fetal or neonatal complications are less consistent. The first possible report of harm came from an epidemiologic evaluation of Medicaid data of 29,507 infants born between 1985 and 2000,[67] which demonstrated that the risks of major congenital malformations, predominantly cardiovascular and neurologic abnormalities, were significantly increased among infants exposed to an ACEi in the first trimester compared to those without exposure to antihypertensive drugs. However, there were other studies that did not demonstrate such an association with ACEi use in the first trimester, after adjusting for underlying disease characteristics, particularly first-trimester hypertension.[68] However, the limitation of most of the studies that showed a negative association with first-trimester exposure is that they did not account for malformations among miscarriages, pregnancy terminations, or stillbirth. Therefore, the possibility of teratogenesis with first-trimester exposure to an ACEi or ARB cannot be confidently refuted, and caution must be undertaken in prescribing these drugs to women of childbearing age.

It is, therefore, the judgment of the Work Group that for women who are considering pregnancy, ACEi and ARB treatment should be avoided. Likewise, women of childbearing age should be counseled appropriately regarding the risks of ACEi and ARB exposure during pregnancy and the need for effective contraception. Women who become pregnant while on RAS blockade treatment should stop ACEi/ARB treatment immediately and should be monitored for fetal and neonatal complications.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping the ACEi or ARB immediately (Figure 4).

The cardiovascular and kidney benefits of ACEi and ARB treatment in patients with CKD and diabetes, hypertension, and albuminuria warrant efforts to maintain patients on these drugs, when possible. Hyperkalemia is a known complication with RAS blockade and occurs in up to 10% of outpatients[69] and up to 38% of hospitalized patients[70] receiving an ACEi. Risk factors for the development of hyperkalemia with the use of drugs that inhibit the RAS included CKD, diabetes, decompensated congestive heart failure, volume depletion, advanced age, and use of concomitant medications that interfere with kidney potassium excretion.[71] Patients with these risk factors, however, are also the same population who would be expected to derive the greatest cardiovascular and kidney benefits from these drugs. Although there are no RCTs testing the benefits and harms of mitigating hyperkalemia in order to continue RAS blockade therapy, stopping RAS blockers or reducing the RAS blocker dose has been associated with increased risk of cardiovascular events in observational studies.[72,73]

Therefore, identifying patients at risk of hyperkalemia and instituting preventive measures should allow these patients to benefit from RAS blockade.

Measures to control high potassium levels include the following[74]:

- Moderate potassium intake, with specific counseling to avoid potassium-containing salt substitutes[75] or food products containing the salt substitutes.
- Review the patient's current medication and avoid drugs that can impair kidney excretion of potassium. History of the use of over-the-counter nonsteroidal anti-inflammatory drugs, supplements, and herbal treatments should be pursued, and patients should be counseled to discontinue these remedies if present.
- General measures to avoid constipation should include sufficient fluid intake and exercise.
- Initiate diuretics treatment to enhance the excretion of potassium in the kidneys.[69,76–81] Diuretics can precipitate acute kidney injury (AKI) and electrolyte abnormalities, and the hypokalemic response to diuretics is diminished with low eGFR and depends on the type of diuretic used. Diuretics are most compelling for hyperkalemia management when there is concomitant volume overload or hypertension.
- Treatment with oral sodium bicarbonate is an effective strategy in minimizing the risk of hyperkalemia in patients with CKD and metabolic acidosis.[82] Concurrent use with diuretics will reduce the risk of fluid overload that can occur from sodium bicarbonate treatment.
- Treatment with potassium binders, such as patiromer or sodium zirconium cyclosilicate, where each has been used to treat hyperkalemia associated with RAS blockade therapy for up to 12 months.[83,84] Such treatment may be considered when the above measures fail to control serum potassium levels. Both studies demonstrated the effectiveness of achieving normokalemia and that treatment with RAS blockade agents can be continued without treatment-related serious adverse effects. However, clinical outcomes were not evaluated; efficacy and safety data beyond 1 year of treatment are not available; and cost and inaccessibility to the drugs in some countries remain barriers to their utilization.

For the various interventions to control high potassium, pre-existing polypharmacy, costs, and patient preferences should be considered when choosing among the options.

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

The dose of an ACEi or ARB should be reduced or discontinued only as a last resort in patients with hyperkalemia after the measures outlined above have failed to achieve a normal serum potassium level. Similar efforts should be made to discontinue other concurrent blood pressure medication before attempting to reduce the ACEi or ARB dose in patients who experience symptomatic hypotension.

When these drugs are used in patients with eGFR <30 ml/min per 1.73 m^2, close monitoring of serum potassium level is required. Withholding these drugs solely on the basis of the level of kidney function will unnecessarily deprive many patients of the cardiovascular benefits they otherwise would receive, particularly when measures could be undertaken to mitigate the risk of hyperkalemia. However, in patients with advanced CKD who are experiencing uremic symptoms or dangerously high serum potassium levels, it is reasonable to discontinue ACEi and ARB treatment temporarily with the aim of resolving any hemodynamic reductions in eGFR and reducing symptoms to allow time for kidney replacement therapy preparation.

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

Combination therapy with ACEi, ARBs, or direct renin inhibitors reduces blood pressure and albuminuria to a larger extent than does monotherapy with these agents. Long-term outcome trials in patients with diabetes and CKD demonstrated no kidney or cardiovascular benefit of RAS blockade with combined therapy to block the RAS versus the single use of RAS inhibitors. However, combination therapy was associated with a higher rate of hyperkalemia and AKI,[85,86] and thus only one agent at a time should be used to block the RAS.

Research recommendations

RCTs are needed to evaluate the following:

- The effect of ACEi or ARB treatment in patients with diabetes, elevated albuminuria, and normal blood pressure on the outcomes of albuminuria reduction, progression of diabetes and CKD, and development of kidney failure.
- Clinical benefits and harms of mitigating hyperkalemia during RAS blockade, compared with forgoing RAS blockade.
- Decision aids for hyperkalemia risk and testing during initiation and dose titration of RAS blockers would inform monitoring algorithms.

1.3 Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

Patients with T2D and CKD are at increased risk of both cardiovascular events and progression to kidney failure. Thus, preventive treatment strategies that reduce the risk of both adverse kidney and cardiovascular outcomes are paramount. There is substantial evidence confirming that SGLT2i confer significant kidney and heart protective effects in these patients. This was demonstrated in:

(i) Three large RCTs reporting on efficacy for primary cardiovascular outcomes and secondary kidney outcomes among patients with T2D: the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) trial, the CANagliflozin cardioVascular Assessment Study (CANVAS), and the Dapagliflozin Effect on

CardiovascuLAR Events [DECLARE-TIMI 58] trial.[87–90] Subsequently, there was an additional RCT of patients with T2D and ASCVD that found non-inferiority for cardiovascular outcomes with an SGLT2i, including among CKD subgroups (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial [VERTIS CV][91]).

(ii) A meta-analysis of these 3 cardiovascular outcome trials (EMPA-REG, CANVAS, DECLARE-TIMI 58) that was stratified by CKD subgroups[92]; this analysis was conducted before VERTIS CV was published.

(iii) Two RCTs that specifically enrolled a CKD population and were designed to evaluate primary kidney outcomes but also reported on secondary cardiovascular outcomes; (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE],[93] and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD][94]). A third RCT, The Study of Heart and Kidney Protection With Empagliflozin (EMPA-Kidney), also enrolled an exclusive CKD population to evaluate a composite cardio-kidney outcome and was stopped early due to clear efficacy, but full study results have not been published yet.[95] DAPA-CKD and EMPA-KIDNEY enrolled patients with or without T2D.

(iv) A primary cardiovascular outcome RCT that exclusively enrolled patients with diabetes and CKD (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk [SCORED][96]).

(v) A meta-analysis of 4 trials (EMPA-REG, CANVAS, CREDENCE, DECLARE-TIMI 58) evaluating kidney outcomes[97]; another later meta-analysis evaluating cardiovascular and kidney outcomes that also included VERTIS CV for 5 total trials[98]; and another meta-analysis[99] of cardiovascular outcomes among the 3 trials that enrolled an exclusive CKD population (CREDENCE, DAPA-CKD, and SCORED).

(vi) Four RCTs that enrolled patients with heart failure evaluating primary cardiovascular outcomes, but also reported on secondary kidney outcomes. Two of these trials enrolled patients with heart failure and reduced ejection fraction (HFrEF) among adults with and without T2D (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure [DAPA-HF][100] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction [EMPEROR-Reduced][101]). These trials also stratified by eGFR (<60 and ≥60 ml/min per 1.73 m^2) (Figure 5). One trial enrolled patients with heart failure and preserved ejection fraction (HFpEF) with and without T2D (The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [EMPEROR-Preserved]).[102] Another trial enrolled patients with diabetes with recent acute hospitalized heart failure with or without reduced ejection fraction (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure [SOLOIST-WHF]).[103]

SGLT2i lower blood glucose levels by inhibiting kidney tubular reabsorption of glucose. They also have a diuretic effect, as the induced glycosuria leads to osmotic diuresis and increased urine output. SGLT2i also appear to alter fuel metabolism, shifting away from carbohydrate utilization to ketogenesis. In a prior meta-analysis of 45 RCTs, SGLT2i conferred modest lowering of HbA1c (mean difference 0.7%), lowering of systolic blood pressure (4.5 mm Hg), and weight loss (–1.8 kg).[104] However, despite these relatively modest, albeit favorable, improvements in cardiovascular risk factors, SGLT2i demonstrated substantial reductions in both composite cardiovascular outcomes and composite kidney outcomes. The cardiovascular and kidney benefits appear independent of glucose-lowering, suggesting other mechanisms for organ protection, such as reduction in intraglomerular pressure and single-nephron hyperfiltration leading to preservation of kidney function.[105]

The DAPA-CKD[94] and SCORED[96] trials enrolled CKD patients with an eGFR down to as low as 25 ml/min per 1.73 m^2. The EMPEROR-Reduced[101] and EMPEROR-Preserved[102] trials, although not an exclusive CKD population, did allow enrollment of patients with an eGFR as low as 20 ml/min per 1.73 m^2. There has been no evidence of effect modification for the effect of the drug based on the population (i.e., with/without heart failure and by GFR levels). The EMPA-Kidney trial, although not yet published, also enrolled patients with an eGFR as low as 20 ml/min per 1.73 m^2 and was stopped early due to clear evidence of efficacy.[95]

Currently, the safety and efficacy of initiating SGLT2i for people with an eGFR <20 ml/min per 1.73 m^2, in kidney transplant recipients, or among individuals with T1D, are not established and are currently being studied; further studies will help clarify the kidney and cardiovascular benefits among these subgroups.

Recommendation 1.3.1: 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)*.

This recommendation places a high value on the kidney and heart protective effects of using an SGLT2i in patients with T2D and CKD, and a lower value on the costs and adverse effects of this class of drug. The recommendation is strong because in the judgment of the Work Group, all or nearly all well-informed patients would choose to receive treatment with an SGLT2i.

Key information

Balance of benefits and harms. Details for cardiovascular, heart failure, and kidney outcomes are summarized below.

Cardiovascular outcomes. The EMPA-REG trial enrolled over 7000 patients with T2D, baseline glycated hemoglobin (HbA1c) of 7%–10%, established CVD (almost 100%), and an eGFR of at least 30 ml/min per 1.73 m^2.[101] Of these, 1819

	KIDNEY TRIALS			CARDIOVASCULAR TRIALS	
	CREDENCE	**DAPA-CKD**	**EMPA-KIDNEY**	**EMPA-REG**	**CANVAS**
Drug	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Empagliflozin 10 mg, 25 mg once daily	Canagliflozin 100 mg, 300 mg once daily
Total of participants	4401	4304	6609	7020	10,142
% with CVD	50	37.4	27	100	66
eGFR criteria for enrollment (ml/min per 1.73 m^2)	30–90	25–75	≥20–<45 or ≥45–<90	≥30	≥30
Mean eGFR at enrollment (ml/min per 1.73 m^2)	56	43	37.5	74	76
% with eGFR <60	59	88	No information [<45: 5185 (78%); ≥45: 1424 (22%)]	26	20
ACR	Criteria: ACR >300–5000 mg/g [>30–500 mg/mmol] Median ACR 927 mg/g [92.7 mg/mmol]	ACR 200–5000 mg/g [20–500 mg/mmol] ACR Median DAPA: 965 mg/g [96.5 mg/mmol]; Placebo: 934 mg/g [93.4 mg/mmol]	eGFR ≥45–<90: ACR ≥200 mg/g [≥20 mg/mmol] (or PCR ≥300 mg/g [≥30 mg/mmol]) No ACR criteria for eGFR ≥40–<45 Median ACR 412 mg/g [41.2 mg/mmol]	No criteria ACR <30 mg/g [<3 mg/mmol] in 60%; 30–300 mg/g [3–30 mg/mmol] in 30%; >300 mg/g [>30 mg/mmol] in 10%	No criteria Median ACR 12.3 mg/g [1.23 mg/mmol]
Follow-up (yr)	2.6	2.4	Expected ≥3	3.1	2.4
Primary outcome(s)	Composite of kidney failure, doubling of SCr, or death from kidney or CV causes	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from kidney or CV causes	First occurrence of a composite of kidney disease progression (kidney failure, sustained decline in eGFR to <10 ml/min/1.73 m^2, sustained decline in eGFR ≥40%, or renal death) or CV death	MACE	MACE
CV outcome results	CV death, MI, stroke: HR: 0.80; 95% CI: 0.67–0.95; hospitalization for HF: HR: 0.61; 95% CI: 0.47–0.80	Secondary composite of CV death or hospitalization for HF: HR: 0.71; 95% CI: 0.55-0.92	Not reported	MACE: HR: 0.86; 95% CI: 0.74–0.99; hospitalization for HF: HR 0.65; 95% CI: 0.50–0.85	MACE: HR: 0.86; 95% CI: 0.75–0.97; hospitalization for HF: HR 0.67; 95% CI: 0.52–0.87
Kidney outcome	Composite of kidney failure, doubling SCr, or death from kidney or CV causes	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from kidney or CV causes	First occurrence of kidney failure, sustained decline in eGFR to <10 ml/min/1.73 m^2, sustained decline in eGFR ≥40%, or renal death	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or renal death) and incident albuminuria	Composite doubling in SCr, kidney failure, or death from kidney causes
Kidney outcome results	Primary kidney: HR: 0.70; 95% CI: 0.59–0.82	Primary outcome: HR: 0.61; 95% CI: 0.51– 0.72	[Trial stopped early due to positive results]	Incident/worsening nephropathy: 12.7% vs. 18.8% in empagliflozin vs. placebo. [HR: 0.61; 95% CI: 0.53–0.70] Incident albuminuria: NS	Composite kidney: 1.5 vs. 2.8 per 1000 patient-years in the canagliflozin vs. placebo [HR: 0.53; 95% CI: 0.33–0.84]

Figure 5 | Cardiovascular and kidney outcome trials for sodium–glucose cotransporter-2 inhibitors (SGLT2i). ACR, albumin-creatinine ratio; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; KRT, kidney replacement therapy; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not applicable; NS, not significant; PCR, protein-creatinine ratio; SCr, serum creatinine; T2D, type 2 diabetes. (Continued)

	CARDIOVASCULAR TRIALS			HEART FAILURE TRIALS				
	DECLARE-TIMI 58	**VERTIS-CV**	**SCORED**	**DAPA-HF**	**EMPEROR-Reduced**	**SOLOIST**	**EMPEROR-Preserved**	**DELIVER**
Drug	Dapagliflozin 10 mg once daily	Ertugliflozin 5mg, 15 mg once daily	Sotagliflozin 200 mg, 400 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Sotagliflozin 200 mg, 400 mg once daily	Empagliflozin 10 mg once daily	Dapagliflozin 10 mg once daily
Total of participants	17,160	8246	10,584	4744	3730	1222	5988	6263
% with CVD	41	100	100	100	100	100	100	100
eGFR criteria for enrollment (ml/min per 1.73 m^2)	CrCl ≥60, 45% had eGFR 60–90	No criteria	25–60 ml/min per 1.73 m^2	≥30	>20	No criteria	No criteria	≥25
Mean eGFR at enrollment (ml/min per 1.73 m^2)	85	76	44	66	62	50	61	Not reported
% with eGFR <60	7.4	21.9	100	41	48	69.9	49.9	Not reported
ACR	ACR <30 mg/g [<3 mg/mmol] in 69.1%, ≥30 to ≤300 mg/g [≥3–≤30 mg/mmol] in 23.9%, and >300 mg/g [>30 mg/mmol] in 6.9%	No criteria	No criteria ACR <30 mg/g [3 mg /mmol] in 35%; ACR 30–<300 mg/g [3–<30 mg/mmol] in 34%; ACR ≥300 mg/g [≥30 mg/mmol] in 31%	No criteria	No criteria	No criteria	No criteria	No criteria
Follow-up (yr)	4.2	3.5	1.3	1.5	1.3	0.76	2.2	Expected 2.25
Primary outcome(s)	1) MACE; 2) Composite CV death or hospitalization for HF	MACE	Deaths from CV causes, hospitalizations for HF, and urgent visit for HF	CV death or worsening HF	CV death or hospitalization for HF	Deaths from CV causes and hospitalizations and urgent visits for HF	CV death or hospitalization for HF	Time to first occurrence of: CV death, hospitalization for HF, or urgent HF visit
CV outcome results	MACE: HR: 0.93; 95% CI: 0.84–1.03; CV death or hospitalization for HF: HR: 0.83; 95% CI: 0.73–0.95	MACE: HR: 0.97; 95% CI: 0.85–1.11	Primary outcome: HR: 0.74; 95% CI: 0.63–0.88	Primary outcome: HR: 0.74; 95% CI: 0.65–0.85	Primary outcome: HR: 0.75; 95% CI: 0.65–0.86	Primary outcome: HR: 0.67; 95% CI: 0.52–0.85	Primary outcome: HR: 0.79; 95% CI: 0.69–0.90	[Met primary endpoint]
Kidney outcome	Composite of ≥40% decrease in eGFR to <60 ml/min per 1.73 m^2, kidney failure, CV or renal death	Composite of kidney death, kidney replacement therapy, or doubling of SCr	First occurrence of a sustained decrease in GFR ≥50% for ≥30 days, long-term dialysis, kidney transplantation, or a sustained eGFR <15 ml/min per 1.73 m^2 for ≥30 days	Composite of worsening kidney function (sustained decline of eGFR ≥50%, kidney failure, or renal death)	Chronic dialysis or kidney transplant or ≥40% sustained reduction in eGFR or sustained eGFR <15 ml/min per 1.73 m^2 in patients with a baseline eGFR ≥30 ml/min per 1.73 m^2 or sustained eGFR of <10 ml/min per 1.73 m^2 in patients with a baseline GFR of <30 ml/min per 1.73 m^2	Not reported	Composite kidney outcome	Not reported
Kidney outcome results	Composite kidney: HR: 0.76; 95% CI: 0.67–0.87	Composite kidney outcome: HR: 0.81; 95% CI: 0.63–1.04	Composite kidney outcome: HR: 0.71; 95% CI: 0.46–1.08	Composite kidney outcome: HR: 0.71; 95% CI: 0.44–1.16	Composite kidney outcome: HR: 0.50; 95% CI: 0.32–0.77	N/A	Composite kidney outcome: HR: 0.95; 95% CI: 0.73–1.24	Not reported

Figure 5| (Continued)

(25.9%) participants had an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to 10 or 25 mg of empagliflozin versus placebo and followed for a median of 3.1 years. In the overall trial, empagliflozin reduced 3-point major adverse cardiovascular events (MACE) by 14% (HR: 0.86; 95% CI: 0.74–0.99).

Among participants in EMPA-REG with an eGFR of 30–60 ml/min per 1.73 m^2, there was a trend for benefit for the primary cardiovascular outcome that was not statistically significant in this subgroup, but there was no evidence for heterogeneity of treatment effect across all eGFR subgroups (*P*-interaction = 0.20). In a prespecified analysis from EMPA-REG of patients with prevalent kidney disease defined as an eGFR <60 ml/min per 1.73 m^2 and/or an albumin-creatinine ratio (ACR) >300 mg/g [>30 mg/mmol], empagliflozin compared to placebo was associated with reduction in cardiovascular death (HR: 0.71; 95% CI: 0.52–0.98), all-cause mortality (HR: 0.76; 95% CI: 0.59–0.99), and heart failure hospitalization (HR: 0.61; 95% CI: 0.42–0.87).[106]

The CANVAS program, which combined data from 2 RCTs (CANVAS and CANVAS-R) enrolled over 10,000 patients with T2D, HbA1c between 7.0% and 10.5%, and an eGFR of at least 30 ml/min per 1.73 m^2.[87] Approximately two-thirds (66%) of participants had established CVD, and 2039 (20.1%) had CKD with an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to canagliflozin 100 or 300 mg per day versus placebo and followed for a median of 2.4 years. As in EMPA-REG, the SGLT2i canagliflozin also reduced MACE by 14% (HR: 0.86; 95% CI: 0.75–0.97).

In subgroup analyses from the CANVAS trial, those with an eGFR of 30–60 ml/min per 1.73 m^2 also experienced cardiovascular benefit for the primary MACE outcome (HR: 0.70; 95% CI: 0.55–0.90), with no evidence of heterogeneity of treatment effect by eGFR status (*P*-interaction = 0.20).

The DECLARE-TIMI 58 trial enrolled 17,160 participants with an HbA1c level of 6.5%–12%. Only 41% had established CVD; the other 59% had multiple cardiovascular risk factors, so it was largely a primary prevention trial.[89] Although creatinine clearance of ≥60 ml/min was an eligibility criterion, there were 1265 participants (7.4%) who had an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to dapagliflozin 10 mg per day versus placebo and followed for a median of 4.2 years. In the main trial, dapagliflozin met its primary safety endpoint of noninferiority for MACE, but superiority for MACE (1 of 2 primary endpoints) did not reach statistical significance. However, dapagliflozin did reduce the second primary efficacy outcome of cardiovascular death or hospitalization for heart failure (HR: 0.83; 95% CI: 0.73–0.95).[89] There was also no evidence of heterogeneity by eGFR subgroups of primary efficacy outcomes of cardiovascular death or heart failure hospitalization (*P*-interaction = 0.37) or MACE outcome by eGFR subgroups (*P*-interaction = 0.99).

The VERTIS CV trial enrolled 8246 patients with T2D and ASCVD (22% of participants had eGFR <60 ml/min per 1.73 m^2) and demonstrated non-inferiority of ertugliflozin versus placebo for the primary outcome of 3-point MACE.[91] While there was a trend for benefit for the key secondary endpoint of cardiovascular death or heart failure hospitalization, this did not meet statistical significance (HR: 0.88; 95% CI: 0.75–1.03). There was no significant interaction for either the primary or secondary cardiovascular outcomes when stratified by CKD subgroups.

In the CREDENCE trial among patients with T2D with albuminuric CKD (discussed further below for primary kidney outcome), canagliflozin reduced the risk of the secondary cardiovascular outcomes of hospitalization for heart failure and MACE by 39% (HR: 0.61; 95% CI: 0.47–0.80) and 20% (HR: 0.80; 95% CI: 0.67–0.95), respectively.[93]

In the DAPA CKD trial which enrolled patients with albuminuric CKD with and without T2D (discussed further below for primary kidney outcome), dapagliflozin reduced the risk of the secondary cardiovascular outcome of death from cardiovascular cause or hospitalization for heart failure by 29% (HR: 0.71; 95% CI: 0.55–0.92).[94]

The SCORED trial, which enrolled patients with T2D and CKD, was ended early due to loss of funding.[96] The primary cardiovascular endpoint was changed during the trial to a composite of cardiovascular death, heart failure hospitalizations, or urgent visits for heart failure. Sotagliflozin reduced this primary outcome by 26% (HR: 0.74; 95% CI: 0.63–0.88); of note, sotagliflozin also reduced the original coprimary endpoint of cardiovascular death and heart failure hospitalizations by 23% (HR: 0.77; 95% CI: 0.66–0.91).

The number of participants with T2D and CKD (eGFR 30 to <60 ml/min per 1.73 m^2) and the number of events were relatively small across all these trials. Thus, a 2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58 trials and examined cardiovascular outcomes among individuals with and without CKD.[92] For those trial participants with an eGFR of 30 to <60 ml/min per 1.73 m^2, an SGLT2i similarly reduced the risk of hospitalization for heart failure (HR: 0.60; 95% CI: 0.47–0.77) and MACE (HR: 0.82; 95% CI: 0.70–0.95).

Another meta-analysis examined the pooled effects of the 3 trials that enrolled an exclusively CKD population (CREDENCE, DAPA-CKD, and SCORED) and confirmed the benefit of SGLT2i for reducing the composite cardiovascular outcome of heart failure hospitalizations or cardiovascular death (HR: 0.73; 95% CI: 0.65–0.82).[99]

Heart failure outcomes. In the original cardiovascular outcome trials with SGLT2i among patients with T2D, there was a significant reduction in the risk of hospitalizations for heart failure that was consistent across all 3 trials (EMPA-REG, CANVAS, and DECLARE-TIMI 58). This result was also confirmed in a real-world registry, with the reduction in risk of hospitalization for heart failure and cardiovascular death associated with SGLT2i, mirroring the favorable

benefits seen in the RCTs.[107] This led to dedicated trials of SGLT2i specifically among patients with heart failure.

The DAPA-HF trial enrolled 4744 patients with symptomatic HFrEF defined as ejection fraction ≤40%, with an eGFR ≥30 ml/min per 1.73 m^2 (mean eGFR 66 ml/min per 1.73 m^2), including 55% of individuals without diabetes.[100] Over a median of 18.2 months, the primary outcome of cardiovascular death, heart failure hospitalization, or urgent heart failure visit occurred in 16.3% of the dapagliflozin group and 21.2% of the placebo group (HR: 0.74; 95% CI: 0.65–0.85). The primary outcome was similarly reduced for individuals with or without diabetes, with no effect of heterogeneity by diabetes status. The primary outcome was also similar among those with an eGFR ≥60 ml/min per 1.73 m^2 (HR: 0.76; 95% CI: 0.63–0.92) or <60 ml/min per 1.73 m^2 (HR: 0.72; 95% CI: 0.59–0.86). This finding suggests a potential role for cardiovascular benefit among CKD patients with HFrEF, even without the presence of diabetes.

The EMPEROR-Reduced trial enrolled 3730 patients with HFrEF, defined as ejection fraction ≤40%, with an eGFR ≥20 ml/min per 1.73 m^2 (mean eGFR 62 ml/min per 1.73 m^2), including 50% of individuals with T2D.[101] Over a median of 16 months, the primary outcome of cardiovascular death or heart failure hospitalization occurred in 19.4% of the empagliflozin group and 24.7% of the placebo group (HR: 0.75; 95% CI: 0.65–0.86). As seen in DAPA-HF, the primary outcome was similarly reduced for individuals with and without diabetes. The primary outcome among those with an eGFR ≥60 ml/min per 1.73 m^2 was HR: 0.67; 95% CI: 0.55–0.83 and for those with eGFR <60 ml/min per 1.73 m^2 was HR: 0.83; 95% CI: 0.69–1.00. A composite kidney outcome HR of 0.50 (95% CI: 0.32–0.77) was also reported.

A recent meta-analysis of both the DAPA-HF and EMPEROR-Reduced trials further revealed a composite outcome on first hospitalization for heart failure or cardiovascular death of HR: 0.72 (95% CI: 0.62–0.82) for an eGFR ≥60 ml/min per 1.73 m^2 and HR: 0.77 (95% CI: 0.68–0.88) for eGFR <60 ml/min per 1.73 m^2; a composite kidney outcome HR: 0.62; 95% CI: 0.43–0.90 ($P = 0.013$) was also reported.[108]

The EMPEROR-Preserved trial enrolled 5988 patients, with or without T2D, with class II-IV heart failure symptoms and an ejection fraction ≥40%.[102] Empagliflozin, compared to placebo, reduced the risk of the primary outcome of cardiovascular death or hospitalization for heart failure by 21% (HR: 0.79; 95% CI: 0.69–0.90). This benefit was again similar among patients with or without diabetes. Fifty percent of study participants had an eGFR <60 ml/min per 1.73 m^2, and there was no significant interaction by eGFR status (≥60 vs. <60 ml/min per 1.73 m^2) for the primary cardiovascular outcome.

The SOLOIST trial enrolled patients with T2D who had recently been hospitalized for worsening heart failure (with or without reduced ejection fraction), of which 70% of patients had an eGFR <60 ml/min per 1.73 m^2.[103] The primary outcome was deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial was stopped early, but sotagliflozin did reduce the primary outcome by 33% (HR: 0.67; 95% CI: 0.52–0.85). There was no significant interaction by eGFR status for the primary outcome.

The ongoing phase III Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER) trial randomized patients with heart failure with mildly reduced or preserved ejection fraction (left ventricular ejection fraction [LVEF] >40%) with or without T2D to treatment with dapagliflozin 10 mg or placebo. On May 5, 2022, it was announced that the results reached a statistically significant and clinically meaningful reduction in the primary composite endpoint of cardiovascular death or worsening heart failure. Results are expected to be reported later in 2022.

Kidney outcomes. EMPA-REG (empagliflozin vs. placebo) also evaluated a prespecified kidney outcome of incident or worsening nephropathy, defined as progression to severely increased albuminuria (ACR >300 mg/g [>30 mg/mmol]), doubling of serum creatinine, accompanied by an eGFR ≤45 ml/min per 1.73 m^2, initiation of kidney replacement therapy, or death from kidney causes (i.e., "renal death"). This incident or worsening nephropathy outcome was lower in the empagliflozin group—12.7% versus 18.8%—with a HR of 0.61 (95% CI: 0.53–0.70).[105]

In the CANVAS program (overall cohort including those with and without baseline CKD), canagliflozin also conferred kidney benefit, with a 27% lower risk of progression of albuminuria (HR: 0.73; 95% CI: 0.67–0.79) and a 40% lower risk of a composite kidney outcome (≥40% reduction in eGFR, need for kidney replacement therapy, or death from kidney cause; HR: 0.60; 95% CI: 0.47–0.77).[87] The CANVAS program further reported additional prespecified kidney outcomes.[88] The composite kidney outcome of doubling of serum creatinine, kidney failure, and death from kidney causes occurred in 1.5 versus 2.8 per 1000 patient-years in the canagliflozin versus placebo groups (HR: 0.53; 95% CI: 0.33–0.84). There was also a reduction in albuminuria and an attenuation of eGFR decline.[88]

In the DECLARE-TIMI 58 trial (dapagliflozin vs. placebo), there was a 1.3% absolute and 24% relative risk reduction in the secondary kidney outcome (a composite of a ≥40% decrease in eGFR to <60 ml/min per 1.73 m^2, kidney failure, and cardiovascular death or death from kidney causes: HR: 0.76; 95% CI: 0.67–0.87).[89] In the DAPA-HF trial, the secondary outcome of worsening kidney function (defined as a sustained ≥50% reduction in eGFR, kidney failure, or death from kidney causes) occurred in 1.2% of the dapagliflozin arm and 1.6% of the placebo arm (HR: 0.71; 95% CI: 0.44–1.16), which was not statistically significant ($P = 0.17$).[100,109] However, the median duration of the DAPA-HF trial was only 18.2 months, which may not have been long enough to accumulate kidney endpoints.

The aforementioned 2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58

trials and examined kidney outcomes among individuals with and without CKD.[92] For those trial participants with an eGFR of 30 to <60 ml/min per 1.73 m^2, SGLT2i reduced the risk of adverse kidney outcomes (composite worsening kidney failure, kidney failure, or death from kidney causes; HR: 0.67; 95% CI: 0.51–0.89).

In the VERTIS CV trial, there was a trend for benefit for the secondary kidney outcome which was a composite of death from kidney causes, kidney replacement therapy, or doubling of the serum creatinine, which was not statistically significant (HR: 0.81; 95% CI: 0.63–1.04).[91]

In the aforementioned cardiovascular outcome trials, kidney events were secondary outcomes and not the primary focus. Furthermore, although the above meta-analysis suggested consistent results in subgroup categories of lower kidney function, it also appeared to suggest some attenuation of kidney benefit as the eGFR worsened, with the largest reductions among those with normal eGFR.[92]

This finding was further explored in the CREDENCE trial, which was the first RCT of an SGLT2i specifically powered for primary kidney outcomes among patients with exclusively albuminuric CKD.[93] The CREDENCE trial enrolled patients with T2D (with an HbA1c level of 6.5%–12.0%) and CKD, defined by an eGFR of 30–90 ml/min per 1.73 m^2 with albuminuria (ACR of 300–5000 mg/g [30–500 mg/mmol]), who were receiving standard of care including a maximum tolerated dose of an ACEi or an ARB. In the CREDENCE trial, 50% of patients had established CVD. Patients were randomized to canagliflozin 100 mg daily or placebo and followed for 2.6 years, with the trial stopping early for superiority as recommended by the Data Safety and Monitoring Committee. The primary kidney outcome was defined as a composite of kidney failure, doubling of serum creatinine, or death from kidney or cardiovascular causes. The primary outcome occurred in 43.2 and 61.2 per 1000 patient-years in the canagliflozin and placebo arms respectively, which translated to a 30% relative reduction in the primary kidney outcome by canagliflozin (HR: 0.70; 95% CI: 0.59–0.82). Even for the secondary outcome of dialysis, kidney transplant, or death from kidney causes, there was evidence for significant benefit (HR: 0.72; 95% CI: 0.54–0.97). There was no evidence of heterogeneity of treatment benefit of subgroups defined by eGFR or ACR (*P*-interactions were nonsignificant).

DAPA-CKD was the second SGLT2i trial with a primary kidney outcome.[94] DAPA-CKD enrolled 4304 participants with or without T2D who had an eGFR 25–75 ml/min per 1.73 m^2 and an ACR of 200–5000 mg/g (20–500 mg/mmol) and evaluated a primary outcome of a sustained decline in the estimated GFR of at least 50%, kidney failure, or death from kidney or cardiovascular causes. Over a median of 2.4 years, dapagliflozin reduced the primary kidney outcome by 39% (HR: 0.61; 95% CI: 0.51–0.72). Findings were similar among patients with and without T2D.

SCORED enrolled 10,584 participants with T2D and CKD (eGFR 25 to 60 ml/min per 1.73 m^2) and high CVD risk.[96] As described above, the study primary endpoint was modified during the trial, which was stopped early for lack of funding. The secondary composite kidney endpoint of kidney failure or sustained 50% decline in eGFR had a HR of 0.71 (95% CI: 0.46–1.08).

In addition to the composite kidney outcomes, SGLT2i conferred less annual eGFR decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[88,93,105,110] An updated 2019 meta-analysis pooled data from the 4 major RCTs of SGLT2i that evaluated major kidney outcomes (EMPA-REG, CANVAS, CREDENCE, and DECLARE-TIMI 58).[97] This analysis, which included nearly 39,000 participants with T2D, found that SGLT2i significantly reduced the risk of dialysis, kidney transplant, or death from kidney causes by 33% (RR: 0.67; 95% CI: 0.52–0.86). There was also reduction in kidney failure and AKI. The benefits of SGLT2i on kidney outcomes were seen across all eGFR subgroups,[97] including those with an eGFR of 30–45 ml/min per 1.73 m^2.

In real-world registry data, after propensity matching, the initiation of SGLT2i was associated with a 51% reduced risk of composite kidney outcome of 50% eGFR decline or kidney failure (HR: 0.49; 95% CI: 0.35–0.67). This finding suggests that the kidney benefits seen in clinical trials are generalizable to clinical practice.[111]

It should be noted that there is another RCT that should be informative. The Study of the Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) (NCT03594110) enrolled patients with and without T2D with CKD with either an eGFR ≥20 to <45 ml/min per 1.73 m^2 or an eGFR ≥45 to <90 ml/min per 1.73 m^2 with ACR ≥200 mg/g [≥20 mg/mmol].[95] Compared to the prior CKD trials, this trial included non-albuminuric CKD and enrolled patients with a lower eGFR down to ≥20 ml/min per 1.73 m^2. The primary outcome is a combined cardio-kidney outcome defined as either kidney disease progression (kidney failure, a sustained decline in eGFR to <10 ml/min per 1.73 m^2, death from kidney causes, or a sustained decline of ≥40% in eGFR from randomization) or cardiovascular death. The trial has been stopped due to positive results and will be reported in late 2022.

Harms. There is an increased risk of diabetic ketoacidosis conferred by SGLT2i; however, this is generally a rare event in T2D, occurring in <1 per 1000 patient-years in a prior meta-analysis.[92] In the CREDENCE trial, this was 2.2 versus 0.2 per 1000 patient-years for canagliflozin versus placebo.[93]

In the CANVAS trial, but not the CANVAS-R trial, there was a higher rate of fractures attributed to canagliflozin.[92] Of note, in the CREDENCE trial, which evaluated 100 mg/d of canagliflozin, there was no excess fracture rate.[93]

There is an increased risk of genital mycotic infections with SGLT2i treatment in both men and women that is consistent across all trials. In the CREDENCE trial, which was conducted in a population of patients with exclusively T2D and CKD, this occurred in 2.27% of those in the canagliflozin arm versus 0.59% of those receiving placebo.[93] Most of the time, such infections can be managed with topical antifungal

medications.[112] Self-care practices, such as daily bathing, may reduce risk of genital mycotic infections.

The increased risk of lower-limb amputations seen with canagliflozin in the CANVAS trial[87] was not reproduced in the CREDENCE trial,[93] even though this trial did implement special attention to foot care for prevention. This risk of amputations was also not seen with other SGLT2i (empagliflozin and dapagliflozin). Thus, it remains unclear whether the increased risk of lower-limb amputation in the CANVAS program was due to differing trial populations or protocols, or to chance. However, during the CREDENCE trial recruitment, an amendment was introduced, excluding those at risk for amputation. In the DAPA-HF trial, major hypoglycemia, lower-limb amputation, and fracture occurred infrequently and the incidences were similar between the 2 treatment groups.[100] Meta-analyses have suggested significant heterogeneity across trials, with increased risk of amputation limited to the CANVAS trial and no increased risk associated with the SGLT2i class of medications overall.[113] Observational data have been inconclusive.[114,115] Routine preventive foot care and adequate hydration may reduce risk of foot complications, as well as caution regarding the use of SGLT2i in patients with previous history of amputation.

In the DAPA CKD trial, which enrolled exclusively patients with CKD, the incidence of serious adverse events was similar between the dapagliflozin and placebo treated groups. No diabetic ketoacidosis or severe hypoglycemia was seen among patients without T2D.

In the SCORED trial, which also enrolled an exclusively CKD population, diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than placebo. It should be noted that sotagliflozin is a unique agent that is both an SGLT1i and an SGLT2i. Furthermore, sotagliflozin is not currently available for commercial use.

Quality of evidence. The overall quality of the evidence is high. This recommendation comes from high-quality data consisting of double-blinded, placebo-controlled RCTs of SGLT2i that enrolled a subset of patients with CKD glomerular filtration rate category (G)1–G3b (eGFR ≥30 ml/min per 1.73 m^2), a pooled meta-analysis of RCTs combining efficacy data for this CKD subset. There were 3 RCTs that enrolled exclusively patients with CKD, of which 2 had a primary kidney composite outcome and also reported on secondary cardiovascular outcomes. One additional trial (EMPA-KIDNEY) had a combined cardio-kidney outcome, was stopped early for efficacy, and should report results soon. From these data, there is moderate- to high-quality evidence that SGLT2i treatment reduces undesirable consequences in patients with T2D and CKD, specifically cardiovascular death, hospitalization for heart failure, and progression of CKD to kidney failure. An update to the 2018 Cochrane systematic review and meta-analysis conducted by the ERT identified high-quality evidence for most critical and important outcomes, except for hypoglycemia requiring third-party assistance, fractures, and HbA1c level, due to imprecision or study limitations (Supplementary Table S6[87,89,93,96,116–128]).[129]

- *Study design:* As discussed, there have now been 4 RCTs[87,89,90,93] and a meta-analysis of 4 of these trials[97] that have confirmed the significant benefits of SGLT2i on clinically meaningful kidney outcomes beyond just proteinuria as a surrogate marker. Of note, in the CREDENCE and DAPA-CKD trials, kidney outcomes were the primary outcome evaluated.[93,94] Additionally, the ERT identified 25 relevant RCTs in an updated Cochrane systematic review.[89,91,93,96,102,103,109,116–128,130–134]
- *Risk of bias* is low as these RCT studies demonstrated good allocation concealment, and adequate blinding, with complete accounting for most patients and outcome events. In the meta-analysis by Zelniker *et al.*,[92] the authors found that all 3 trials met the criteria for low risk of bias as assessed by the Cochrane tool for examining risk of bias in RCTs. The ERT-updated Cochrane review identified low risk of bias for most outcomes, except for 4 outcomes (fracture, diabetic ketoacidosis, genital infection, HbA1c), which exhibited unclear blinding of outcome assessors for the majority of the included studies.
- *Consistency* is moderate to high, with consistency of kidney benefit across the trials and by baseline eGFR and albuminuria groups.[97] Additionally, the updated Cochrane review conducted by the ERT found no concerns regarding heterogeneity.[129]
- *Indirectness:* The RCT studies directly compared the effect of SGLT2i with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms.
- *Precision* is good, as studies conducted included large numbers of study participants with acceptable event rates, and therefore narrow confidence intervals. The ERT-updated Cochrane review identified serious imprecision for 1 outcome—hypoglycemia requiring third-party assistance—because of a few events, well below the required optimal information size (as a rule of thumb, a value of 300 events, assuming modest effect sizes and baseline risks), resulting in the inability to exclude the minimally important clinical difference.[135]
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. Additionally, funnel plot assessments indicate no concerns regarding publication bias. All trials were funded by the pharmaceutical industry but with transparent reporting of sponsor involvement in study design and conduct.

Values and preferences. The potential benefits from SGLT2i in terms of cardiovascular, heart failure, and kidney outcomes were judged to be critically important to patients. For example, patients with a history of heart failure or at high risk for heart failure might particularly benefit from this class of medications. Additionally, patients who prefer an oral agent over other injectable medication would also favor SGLT2i treatment. The Work Group also judged that there may be patient-specific factors that would reduce the preference for

SGLT2i in specific patients, such as patients at increased risk of volume depletion, genital infections, or lower-limb amputation due to foot ulcerations. People with a history of urinary tract infections also may not prefer this class of medications.

The Work Group judged that nearly all clinically suitable and well-informed patients would choose to receive SGLT2i for the kidney and cardiovascular protective benefits, compared to other treatments or no treatment. Patients at high risk of side effects (such as those above) or those for whom cost, lack of insurance, or lack of local availability is an issue may choose an alternate medication.

Resource use and costs. Economic models have found use of SGLT2i to be a cost-effective strategy among patients with T2D based on its cardiovascular benefits.[136,137] These medications nevertheless are frequently cost-prohibitive for many patients compared to other cheaper oral diabetes medications (notably sulfonylureas) that do not have the same level of evidence for cardiovascular and kidney benefits. However, more recent analyses have shown that cost-effectiveness in the cardiovascular outcomes trials was primarily driven by reducing costs of CKD progression and kidney failure. In an analysis from the DECLARE-TIMI 58 trial, dapagliflozin treatment increased lifetime quality-adjusted life-years (QALYs) and decreased costs of healthcare at a level that met United Kingdom thresholds for cost-effectiveness due to the kidney benefits (64% of QALYs gain).[138] Additionally, analysis of real-world evidence together with cardiovascular outcome trial data found that SGLT2i use was cost-effective in the United States (US), also primarily attributable to kidney benefits, even though costs for SGLT2i were much higher than in the United Kingdom, China, and Canada.[139]

Nevertheless, SGLT2i are cost-prohibitive for many patients. In the US, obtaining reimbursement or preauthorization from insurance companies for SGLT2i coverage places undue burden on healthcare professionals and patients. There are disparities in the insurance coverage for this class of medications and individuals' ability to pay at current costs. Availability of drugs also varies among countries and regions. Thus, treatment decisions must take into account each patient's preference about the magnitude of benefits and harms of treatment alternatives, drug availability in the country, and cost. Ultimately, some patients may not be able to afford these medications and should be guided in making informed decisions about alternatives for T2D and CKD management.

Considerations for implementation. The eGFR threshold for initiation of SGLT2i has changed over time as more evidence of benefit and safety accrues across a broader range of eGFR. Patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 have now been extensively studied in RCTs of SGLT2i. Participants with T2D and an eGFR as low as 30 ml/min per 1.73 m^2 were included in the EMPA-REG, CANVAS, and CREDENCE trials,[87,90,93] and efficacy and safety in these studies were consistent across both eGFR and albuminuria down to this threshold. The DAPA-CKD and SCORED trials enrolled CKD patients with an eGFR down to as low as 25 ml/min per 1.73 m^2.[94,96] The EMPEROR-Reduced and EMPEROR-Preserved trials, although not exclusive CKD populations, did allow enrollment participants with an eGFR as low as 20 ml/min per 1.73 m^2.[101,102] EMPA-KIDNEY, which enrolled an exclusive CKD population and should report results soon, also enrolled participants with an eGFR ≥20 ml/min per 1.73 m^2.

There are now several lines of evidence demonstrating that initiating an SGLT2i in the eGFR range of 20–29 ml/min per 1.73 m^2 is safe and beneficial. Direct evidence is provided by the DAPA-CKD, SCORED, EMPEROR-Reduced, and EMPEROR-Preserved trials, which enrolled such participants by design. In addition, *post hoc* analyses of CREDENCE and DAPA-CKD demonstrated that participants who met eGFR eligibility at screening but subsequently had lower baseline eGFR prior to randomization (<30 ml/min per 1.73 m^2 and <25 ml/min per 1.73 m^2, respectively) experienced similar kidney benefits as those with baseline eGFR above eligibility thresholds.[140,141] For eligibility, DAPA-CKD required albuminuria (≥200 mg/g), and the EMPEROR trials required a clinical diagnosis of heart failure; evidence for initiating an SGLT2i in the eGFR range of 20–29 ml/min per 1.73 m^2 is therefore strongest for patients with albuminuria or heart failure. However, within and across SGLT2i trials, benefits and harms of SGLT2i have been apparent across subgroups defined by eGFR, albuminuria, and the presence or absence of heart failure, and the preponderance of data suggests that SGLT2i are safe and offer kidney and cardiovascular benefits for patients with or without these specific characteristics. Therefore, we recommend treating patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i.

In subgroup analysis from the conducted trials, efficacy and safety were demonstrated independent of age, sex, and race. Thus, this recommendation holds for patients of all ages and races, and both sexes. In addition, efficacy and safety were demonstrated among subgroups with many common comorbidities and independent of concomitant use of medications commonly used in this population, including RASi. Therefore, SGLT2i can and should be added to the regimen of patients with T2D and CKD treated with a RASi. However, long-term follow-up and further collection of real-world data are needed to confirm the effectiveness and potential harms in specific patient populations.

Specifically, there is insufficient evidence evaluating the efficacy and safety of SGLT2i among kidney transplant patients who may be more vulnerable to infections due to their immunosuppressed states; further studies should clarify this issue. Therefore, this recommendation does not apply to kidney transplant recipients (see Practice Point 1.3.7).

A summary of SGLT2i agents with proven kidney or cardiovascular benefits, their Food and Drug Administration (FDA)–approved doses, and dose adjustments as recommended in CKD are described in Figure 7.

Rationale

For patients with CKD with an eGFR ≥20 ml/min per 1.73 m^2, the current KDIGO guideline recommends using an SGLT2i for the purposes of kidney and cardiovascular protection, whereas metformin is still used for glucose control among patients with an eGFR ≥30 ml/min per 1.73 m^2. The recommendation is strong due to the known kidney and/or cardiovascular protective effects in patients with T2D and CKD as shown in high-quality trials, such as EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, SCORED, DAPA-HF, SOLOIST, EMPEROR-Reduced and EMPEROR-Preserved. VERTIS CV showed cardiovascular non-inferiority, as well as safety. In the judgment of the Work Group, nearly all well-informed patients would prefer to receive this treatment over the risks of developing diabetic ketoacidosis, mycotic infections, and foot complications.

As mentioned above, the EMPA-KIDNEY trial will report results by the end of 2022. Once the full trial data are published, KDIGO will incorporate the new data into meta-analyses to provide updated summary estimates of SGLT2i benefits and risks.

The prioritization of SGLT2i therapy in high-risk patients such as those with CKD is consistent with the recommendations from other professional societies including the American College of Cardiology (ACC),[142] the joint statement by the ADA and the European Association of the Study of Diabetes (EASD),[143] and the joint guideline by the European Society of Cardiology (ESC) and EASD.[144] The ADA/EASD statement recommends that patients with T2D who have established ASCVD, CKD, or clinical heart failure be treated with an SGLT2i (or GLP-1 RA) with proven cardiovascular benefit as part of a glucose-lowering regimen independent of HbA1c, but with consideration of patient-specific factors.[145–147]

There is a lack of clarity across guidelines regarding initial therapy for patients not yet treated with a glucose-lowering drug. Most guidelines suggest initial therapy with metformin, whereas the ESC guideline recommends initial therapy with an SGLT2i for patients with high CVD risk. The current KDIGO guideline recommends using an SGLT2i for most patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 and using metformin for patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2. Sequencing of interventions should be individualized to address most pressing individual clinical needs (Section 1.1).

The 2019 ESC guideline provided a Class I recommendation to use SGLT2i for patients with T2D and ASCVD or at high/very high cardiovascular risk (which includes target organ damage such as CKD).[144] The difference between the ESC/EASD recommendation and the current KDIGO recommendation may stem from different judgments about the importance of the population studied in the landmark clinical trials. Thus, the evidence is particularly strong for the population corresponding to the CREDENCE and DAPA-CKD studies (ACR >200–300 mg/g [>20–30 mg/mmol] and eGFR >25–30 and <75–90 ml/min per 1.73 m^2. In contrast, the current evidence benefit seen for patients with less albumin excretion comes from cardiovascular outcome trials with secondary kidney outcomes; however, EMPA-KIDNEY also enrolled patients with CKD without albuminuria, and these results will be informative when published.

The efficacy and safety of SGLT2i has not been established in T1D. Use of SGLT2i treatment in the US remains off-label, as the FDA has not approved its use in T1D. In Europe, the European Commission has approved dapagliflozin and sotagliflozin for use in T1D as an adjunct to insulin in 2019. However, the drugmaker of dapagliflozin withdrew its T1D indication in 2021, citing concerns about diabetic ketoacidosis. Dapagliflozin remains approved in Japan for T1D.

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen (Figure 6[148]).

For patients already being treated with glucose-lowering medications, SGLT2i can be added to the existing medical regimen. The risk of hypoglycemia is low with SGLT2i monotherapy, as the drug-induced glycosuria decreases as blood glucose normalizes, but the risk may be increased when this therapy is used concomitantly with other medications that can cause hypoglycemia, such as sulfonylureas or insulin.[149,150] These therapies may need to be adjusted if the patient's HbA1c is already below the treatment target. However, notably, SGLT2i have been studied among patients without T2D who have CKD in the DAPA-CKD trial (and the soon-to-be-published EMPA-KIDNEY trial) or who have heart failure (in the DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials) and did not confer any increased risk of severe hypoglycemia or diabetic ketoacidosis among individuals without T2D.

For patients not attaining glycemic targets, see Chapter 4 on the management of hyperglycemia.

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Figure 7 shows current FDA-approved doses. As SGLT2i are now indicated for kidney and heart protection, independent of their glucose-lowering effect, the labels have been changed to reflect the studies that include patients with an eGFR >20 ml/min per 1.73 m^2.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

For patients with T2D, there is a small but increased risk of euglycemic diabetic ketoacidosis with SGLT2i (see the Harms section of Recommendation 1.3.1 for more details).

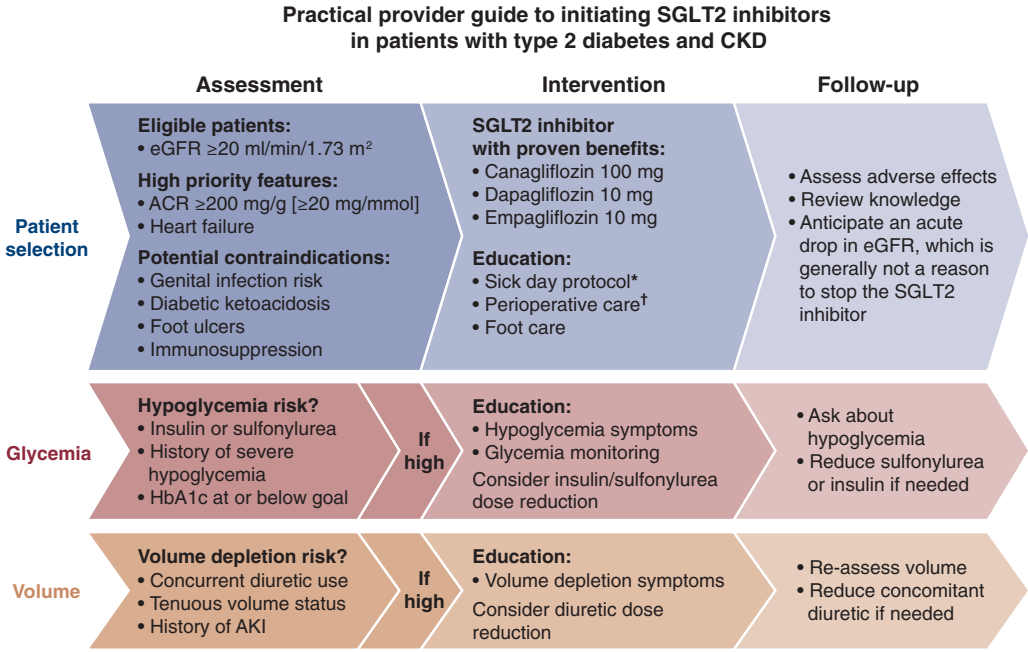


Figure 6 | Practical approach to initiating sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with type 2 diabetes and chronic kidney disease (CKD). *Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold SGLT2i, keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. †Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis; withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required; withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring 1 or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are <1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally. Adapted from Zoungas S, de Boer IH. SGLT2 inhibitors in diabetic kidney disease. *Clin J Am Soc Nephrol*. 2021;16:631–633.[148] Copyright © 2021 by the American Society of Nephrology. ACR, albumin-creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

SGLT2i cause an initial natriuresis with accompanying weight reduction. This may contribute to one of the benefits of these drugs, namely, their consistent reduction in risk for heart failure hospitalizations. However, there is theoretical concern for volume depletion and AKI, particularly among patients treated concurrently with diuretics or who have tenuous volume status. Despite this theoretical concern, clinical trials have shown that the incidence of AKI is decreased with SGLT2i, compared with placebo.[97] Nonetheless, caution is prudent when initiating an SGLT2i in patients with tenuous volume status and at high risk of AKI. For such patients, reducing the dose of diuretics may be reasonable, and follow-up should be arranged to monitor

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m² in DAPA-CKD eGFR ≥30 ml/min per 1.73 m² in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m²
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m² in EMPA-REG eGFR ≥20 ml/min per 1.73 m² in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m² for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m² for HF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m² in CREDENCE	eGFR ≥30 ml/min per 1.73 m²

Figure 7 | Sodium–glucose cotransporter-2 inhibitors (SGLT2i) with established kidney and cardiovascular benefits and dose adjustments as approved by the US Food and Drug Administration (FDA) (take note of country-to-country variation). ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; T2D, type 2 diabetes.

volume status. In older adults, adequate hydration should be encouraged.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

The landmark RCTs demonstrated a reversible decrease in eGFR among those treated with an SGLT2i.[151] However, SGLT2i are associated with overall kidney protection with improved albuminuria, decreased progression to severely increased albuminuria, and reduction of risk from worsening kidney impairment, kidney replacement therapy, or death from kidney causes. Pooled results of the 4 large RCTs that published results on kidney outcomes also demonstrated that risk of AKI is significantly lower with SGLT2i treatment.[97] Therefore, a modest initial drop in eGFR should not necessitate stopping the SGLT2i.

The magnitude of initial drop in eGFR that should be clinically tolerated is not well-defined. *Post hoc* analyses of EMPA-REG OUTCOMES and CREDENCE suggested that a drop in eGFR ≥10% was not associated with increased risk or decreased benefits of empagliflozin and canagliflozin, respectively, compared with a drop in eGFR <10%.[152,153] In CREDENCE, a drop in eGFR ≥30% was uncommon (4% of participants assigned to canagliflozin) but was associated with modestly increased risks of kidney adverse events. Thus, one should tolerate an acute eGFR decrease of ≤30% with initiation of therapy and not discontinue therapy prematurely for an acute eGFR drop within this range. If there is a >30% decline in eGFR, ensure that the patient is not hypovolemic (e.g., adjust diuretic dose), discontinue any other nephrotoxic agents, and evaluate for alternative etiologies for kidney injury.

Practice Point 1.3.6: 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 kidney replacement therapy is initiated.

Protocols of multiple RCTs, including CREDENCE and DAPA-CKD, specified continuation of study drug (active or placebo) even when observed eGFR dropped below the eligibility threshold specified for initiation. Since these protocols provide the evidence base for use of SGLT2i, it is prudent to follow the same approach in clinical care. Very few data are available evaluating use of SGLT2i for patients receiving dialysis, and the glucosuric actions of SGLT2i are likely insignificant with this degree of kidney failure. Therefore, it is reasonable to discontinue an SGLT2i prior to initiation of kidney replacement therapy.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

Research recommendations

- Studies focused on long-term (>5 years) safety and efficacy of SGLT2i treatment among patients with T2D and CKD. We need continued longer safety follow-up data and post-marketing surveillance.
- Studies focused on kidney and heart protective benefits of SGLT2i treatment for patients with T1D.
- Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D and CKD G5.
- Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D who are kidney transplant recipients at high risk of graft loss, CVD, and infection.
- Studies examining the safety and benefit of SGLT2i for patients with CKD and eGFR <20 ml/min per 1.73 m^2 or receiving dialysis.
- Cost-effectiveness analysis of this strategy prioritizing SGLT2i among patients with T2D and CKD, factoring in cardiovascular and kidney benefits against the cost of medications and potential for adverse effects.
- Future work to address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake among low-resource settings.
- Studies examining feasibility and barriers for developing programs to adopt novel therapies such as SGLT2i in clinical practice.
- Real-world studies examining outcomes of patients in health systems that incorporated SGLT2i in the management algorithm of patients with diabetes and kidney disease.

1.4 Mineralocorticoid receptor antagonists (MRA)

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients 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)*.

This recommendation places a high value on the high-quality evidence, from 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), that finerenone, on top of ACEi or ARB treatment, slows progressive loss of eGFR and decreases the risk of a cardiovascular event among people with T2D and albuminuria. It places a relatively lower value on the lack of definitive data regarding adding nonsteroidal MRA to SGLT2i (current standard of care), the risk of hyperkalemia and monitoring of potassium during nonsteroidal MRA treatment, and the lack of observational data evaluating benefits and risks outside of the clinical trial setting. In the judgment of the Work Group, the majority of well-informed patients addressed by the recommendation would

want to receive treatment with a nonsteroidal MRA, but many would not.

Key information

Balance of benefits and harms. Clinical trials have demonstrated the kidney and cardiovascular benefits of RASi use in those with kidney disease. Experimental evidence suggests that RAS blockade leads to incomplete suppression of serum aldosterone levels (aldosterone escape phenomenon), offering an opportunity to consider additional treatment options to lower residual albuminuria and ameliorate kidney fibrosis.[154] Steroidal MRA, such as spironolactone and eplerenone, have established cardiovascular benefits in those with heart failure and are useful for treating primary hyperaldosteronism and refractory hypertension.[155–157] In addition, steroidal MRA reduce albuminuria.[50] However, their effects on kidney disease progression (eGFR decline or kidney failure) have not been examined in larger trials, and hence their benefits on clinical kidney outcomes remains uncertain. Further, the use of steroidal MRA also increases the risk of hyperkalemia (by 2–3 fold) and acute kidney injury (by 2-fold), and spironolactone can cause gynecomastia.[158] These adverse effects along with the report of higher incidence of hyperkalemia after the publication of the Randomized Aldactone Evaluation Study limited the use of these agents in high-risk populations.[159]

Novel nonsteroidal MRA, such as finerenone and esaxerenone, are more selective for mineralocorticoid receptors and have been noted to offer similar reductions in albuminuria but with a lower risk of hyperkalemia.[160,161] Recently, 2 large clinical trials have examined the cardiovascular and kidney effects of finerenone in those with T2D and albuminuria, enrolling patients with serum potassium levels less than 4.8 mmol/l at screening. The FIDELIO-DKD trial included participants with (i) eGFR 25–60 ml/min per 1.73 m^2, ACR 30–<300 mg/g [3–<30 mg/mmol], and diabetic retinopathy or (ii) ACR 300–5000 mg/g [30–500 mg/mmol] and eGFR 25–75 ml/min per 1.73 m^2 (Figure 8). All participants were treated with a RASi, titrated to the maximum antihypertensive or maximum tolerated dose. There was an 18% lower incidence of primary composite outcome that included

	FIDELIO-DKD	FIGARO-DKD
Drug	Finerenone	Finerenone
Total number of participants	5734	7437
% with CVD	45.4	44.7
eGFR and ACR criteria for enrollment	25–<60 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR 25–<75 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]	25–90 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR ≥60 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]
Mean eGFR at enrollment (ml/min per 1.73 m^2)	44	68
% with eGFR <60 ml/min per 1.73 m^2	88.4	38.2
Median ACR at enrollment (mg/g [mg/mmol])	850 [85.0]	309 [30.9]
% with ACR ≥300 mg/g (30 mg/mmol)	87.5	50.7
Follow-up time (median, yr)	2.6	3.4
Primary outcome	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF
Main secondary outcome	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death
Kidney composite outcome result	HR: 0.82; 95% CI: 0.73–0.93	HR: 0.87; 95% CI: 0.76–1.01
Cardiovascular composite outcome result	HR: 0.86; 95% CI: 0.75–0.99	HR: 0.87; 95% CI: 0.76–0.98

Figure 8| Cardiovascular (CV) and kidney outcome trials for finerenone. ACR, albumin-creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

kidney failure, sustained decrease of 40% decline in eGFR, or death from kidney causes with the use of finerenone.[162] While the overall frequencies of adverse events between finerenone and placebo were similar, hyperkalemia-related discontinuation of study drug occurred in 2.3% among those on finerenone (vs. 0.9% in the placebo group).[163]

In the FIGARO-DKD trial, patients with ACR 30–<300 mg/g [3–<30 mg/mmol] and eGFR 25–90 ml/min per 1.73 m^2 or ACR 300–5000 mg/g [30–500 mg/mmol] and eGFR ≥60 ml/min per 1.73 m^2 were included (Figure 8).[164] There was a 13% lower risk of the primary cardiovascular composite outcome, which included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The secondary composite kidney outcome, which included kidney failure, sustained decrease from baseline of at least 40% in eGFR, or death from kidney causes, was not significantly different between finerenone and placebo (HR 0.87, 95% CI 0.76–1.01). Discontinuation of trial regimen was higher among those on finerenone than placebo (1.2% vs. 0.4%).

In a prespecified individual patient-level combined analysis of the FIDELIO and FIGARO trials (including over 13,000 participants), the cardiovascular composite was reduced in those treated with finerenone (HR: 0.86; 95% CI: 0.78–0.95). There was no significant heterogeneity in this cardiovascular benefit according to any reported baseline characteristics, including use of an SGLT2i at baseline (*P*-heterogeneity = 0.41; HR: 0.63; 95% CI: 0.40–<1.00 among 877 participants using an SGLT2i) or use of a GLP-1 RA at baseline (*P*-heterogeneity = 0.63; HR: 0.79; 95% CI: 0.52–1.11 among 944 participants using a GLP-1 RA). There was also a lower incidence of the kidney composite of kidney failure, >57% decrease in eGFR, or death from kidney causes among those treated with finerenone (HR: 0.77; 95% CI: 0.67–0.88), and a lower incidence of kidney failure, defined as initiation of chronic dialysis or kidney transplantation (HR: 0.80; 95% CI: 0.64–0.99).[165]

Similar to finerenone, another nonsteroidal MRA, esaxerenone, has also been shown to lower albumin excretion. However, the long-term kidney and cardiovascular benefits of esaxerenone have not been established, and regulatory approval for esaxerenone is not widespread.[161,166] Hyperkalemia (potassium >6.0 or 5.5 mmol/l) occurred in 9% of the study population treated with esaxerenone.

Quality of evidence. The overall quality of the evidence was rated high, as nonsteroidal MRAs exhibited high-quality evidence of benefit for critical composite outcomes of 4-point MACE, the composite kidney outcome, and sustained eGFR ≥57% or doubling of serum creatinine that are key to clinical decision-making.

In RCTs that compared all MRA with placebo/standard of care (pooled nonsteroidal and steroidal MRA; Supplementary Table S7[50,161,162,164,166–175]), the quality of the evidence was downgraded largely due to limitations evident in the steroidal MRA trials In RCTs that compared steroidal MRA with placebo/standard of care, the quality of the evidence was rated low or very low for most of the critical outcomes, downgraded due to study limitations and serious imprecision. The quality of the evidence was rated moderate for hyperkalemia (Supplementary Table S8[50,161,166–170,172–175])

The rationale for the quality of the evidence for each outcome is detailed below and in Supplementary Table S9.[161,162,164,166–168,171,175] RCTs comparing nonsteroidal MRAs with placebo/standard of care did not report peripheral vascular disease, attainment of HbA1c target, or eGFR.

- *Study design:* Overall, the updated evidence review identified 27 RCTs on MRA, with 5 RCTs comparing nonsteroidal MRA to placebo and/or standard of care.[162,164,166,167,175] FIDELIO-DKD was a large kidney outcome–based trial and FIGARO-DKD was a cardiovascular outcome–based trial respectively.[162,164]
- *Risk of bias* for nonsteroidal MRA is low. FIDELIO-DKD and FIGARO-DKD were well-conducted studies with no risk of bias concerns with appropriate allocation concealment, blinding, and accounting for participants and outcome events. In outcomes that only included the smaller trials,[166,167,175] methodological limitations due to uncertainty in reporting of allocation concealment were evident.
- *Consistency*: The updated Cochrane review found only a concern about heterogeneity for hyperkalemia (defined as K^+ ≥6 mmol/l) with I^2 = 70%. However, the direction of the effect is consistent, and the outcome was only downgraded by 1 level (serious inconsistency).
- *Indirectness:* The RCTs directly compared the effect of nonsteroidal MRA with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms.
- *Precision:* For the critical outcomes of 4-point MACE, composite kidney outcome, and sustained eGFR decrease ≥57% or doubling of serum creatinine exhibited good precision. The outcomes all-cause mortality, kidney failure, and components of 4-point MACE (stroke, myocardial infarction) did indicate benefit but did not exclude the minimally clinical important difference and hence were downgraded 1 level due to serious imprecision. FIDELITY undertook an individual-patient data meta-analysis and found that kidney failure did not exhibit the same imprecision as demonstrated in the updated Cochrane review undertaken by the ERT.[165]
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. The pharmaceutical industry funded all the trials. Transparent reporting and appropriate study conducted were evident in the included trials. Hence, there was no evidence of undue influence of industry involvement in the reporting, protocol, and analyses of the trials.

Values and preferences. The Work Group judged that the majority of well-informed patients with T2D who had persistent albuminuria and normal serum potassium despite receiving the maximal tolerated dose of RAS inhibition, and usually also an SGLT2i, would choose to receive a nonsteroidal MRA with proven kidney and heart protective benefit. Slowing the progression of CKD and reducing risks of cardiovascular events were judged to be critically important to

patients. Factors that may influence some individual patients to not choose treatment with a nonsteroidal MRA include the lack of definitive data on benefits and risks when one is added to an SGLT2i (part of the current standard of care), the limited representation of patients with some relevant characteristics (e.g., moderate albuminuria) in the FIDELIO-DKD and FIGARO-DKD trials, the lack of confirmatory data on benefits and risks in the real-world clinical environment, and the restriction of high-quality data to 1 drug in the drug class.

During the time between initiation and completion of the FIDELIO-DKD and FIGARO-DKD trials, numerous rigorous clinical trials demonstrated large kidney and cardiovascular benefits of SGLT2i (Section 1.3 above), and SGLT2i became an established first-line treatment for T2D with CKD.[143,155] Eligibility criteria for the FIDELIO-DKD and FIGARO-DKD trials define a population for which an SGLT2i is now strongly indicated, and the Work Group judged that nearly all such patients would choose to receive an SGLT2i (*Values and preferences* from Section 1.3 above). An SGLT2i was not required for entry into the FIDELIO-DKD and FIGARO-DKD trials, leaving some uncertainty regarding benefits of using a nonsteroidal MRA on top of SGLT2i, though exploratory analyses suggest that combination therapy is both safe and effective (Practice Point 1.4.2). Direct head-to-head comparisons are not available to test nonsteroidal MRA compared with SGLT2i.

Patients with severely increased albuminuria (ACR ≥300 mg/g [≥30 mg/mmol]), who are at high risk of CKD progression and were best represented in the FIDELIO-DKD trial, might be particularly inclined to choose a nonsteroidal MRA. This recommendation also applies to people with T2D and lower levels of albuminuria (ACR 30–299 mg/g [3–29.9 mg/mmol]), which represent a larger proportion of people with T2D with increased CVD risk but at lower risk of CKD progression.[176–178] The relative and absolute benefits of a nonsteroidal MRA are less clear for this subpopulation. Some patients who meet current serum potassium eligibility criteria for a nonsteroidal MRA (Practice Point 1.4.3) but have a history of severe hyperkalemia or highly variable serum potassium may choose to avoid the added risk of hyperkalemia.

Regulatory approvals for nonsteroidal MRA are recent or pending, and limited data are currently available to confirm the benefits and risks of this class of drugs in routine clinical practice. Only finerenone has been rigorously evaluated with regard to clinical outcomes. Cost may pose a barrier for some patients, particularly when used in combination with other indicated medications, and formal cost-effectiveness evaluations are not yet available.

Resource use and costs. At the time of writing, nonsteroidal MRA are not yet available in many countries and the process of seeking registration with regulatory bodies is underway. Consequently, the cost of these drugs has yet to be determined, but it is very likely that as novel therapeutic agents, they will be priced significantly higher than generic medications. The costs of nonsteroidal MRA may be prohibitive, and therefore their use may have a lower priority in low-resource settings, where efforts will be made to optimize the use of less expensive drugs. Monitoring of potassium during treatment is already indicated for patients with CKD treated with an ACEi or ARB; an increased rate of hyperkalemia may lead to higher healthcare costs due to more frequent patient visits.

Considerations for implementation. Nonsteroidal MRA have been most rigorously tested in patients with CKD and T2D with residual cardiorenal risk, as evidenced by albuminuria (≥30 mg/g [≥3 mg/mmol]) despite treatment with standard of care, including maximal tolerated RAS blockade, and are therefore recommended for this population. So far, only finerenone has demonstrated clinical cardiovascular and kidney benefits. Nonsteroidal MRA can cause hyperkalemia, and treatment dose and monitoring should be in accordance with the clinical trials, as described in Practice Point 1.4.3. Treatment should not be initiated if serum potassium is elevated (4.8 mmol/l was the threshold at screening in the finerenone trials, but per FDA label, serum potassium should not be >5 mmol/l). Most incidents of hyperkalemia can be managed with treatment pauses of 72 hours, as the drug has a short half-life, and if needed, general procedures to manage potassium can be applied as described in Practice Point 1.4.3.

On average, there was only a small reduction in systolic blood pressure (3 mm Hg) with finerenone compared to placebo, and no effect on HbA1c, no increase in hypo- or hyperglycemia, and no sexual side effects due to the specificity for the MRA.[162,164] Beneficial effects of finerenone were similar (no significant heterogeneity) among participants who were also treated with SGLT2i or GLP-1 RA at baseline, and there is potentially a lower risk of hyperkalemia when finerenone is combined with an SGLT2i.[165] This suggests that agents could be combined, but randomized studies have not explicitly tested whether the benefits of these different agents are additive. Steroidal and nonsteroidal MRA should not be combined due to risk of hyperkalemia.

Steroidal MRA are currently contraindicated in pregnancy. For nonsteroidal MRA, there is no experience with pregnancy, so women who are planning for pregnancy or who become pregnant on treatment should have the drug discontinued.

Rationale

Adding an MRA to current standard of care, including ACEi or ARB treatment, has been proven to be an effective strategy to reduce albuminuria in patients with diabetes and CKD. The steroidal MRA, spironolactone and eplerenone, have been shown to effectively reduce albuminuria, but data demonstrating that these MRA reduce the risk of clinical outcomes are not available. The more recently developed nonsteroidal MRA, finerenone and esaxerenone, also reduce albuminuria, and finerenone reduced the risk of kidney and cardiovascular outcomes in 2 pivotal outcome trials.

Practice Point 1.4.1: Nonsteroidal MRA are most appropriate for patients with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

The FIDELIO-DKD and FIGARO-DKD trials enrolled people with T2D and CKD who were treated with standard of care at the time the trials were initiated, which included a RASi and appropriate medications to control glycemia and blood pressure.[162,164] Importantly, eligibility required that participants have albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]) despite these standard interventions. Patients with T2D and albuminuria are known to be at high risk of CKD progression and cardiovascular events, and the FIDELIO-DKD and FIGARO-DKD trials demonstrated that finerenone reduced these events (particularly CKD progression and heart failure) among such patients. Therefore, the most logical application of finerenone is to patients with high residual risks of CKD progression and cardiovascular events, as evidenced by the presence of albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]) despite lifestyle modifications and first-line drug therapies.

Practice Point 1.4.2. A nonsteroidal MRA can be added to a RASi and an SGLT2i for treatment of T2D and CKD.

This guideline issues a strong recommendation for use of an SGLT2i in the treatment of people with T2D and CKD, positioning SGLT2i as first-line drug therapy to prevent CKD progression and cardiovascular events regardless of glycemia (Figures 1 and 2). This recommendation is based on numerous clinical trials that now provide strong evidence of efficacy and safety (see *Balance of benefits and harms* section of Recommendation 1.3.1) and applies to most patients with T2D and CKD for whom a nonsteroidal MRA is also suggested. SGLT2i were not standard of care when the FIDELIO-DKD and FIGARO-DKD trials were initiated. However, 877 participants were using an SGLT2i at baseline, and the cardiovascular effects of finerenone, compared with placebo, appeared to be at least as beneficial among people using versus not using an SGLT2i.[165] It is also possible that SGLT2i may reduce the risk of hyperkalemia for patients treated concomitantly with a RASi and nonsteroidal MRA.[165] These data, combined with complementary mechanisms of action, suggest that the benefits of SGLT2i and finerenone may be additive. Therefore, patients with T2D and CKD who are treated with both a RASi and an SGLT2i and meet criteria for finerenone (including residual albuminuria and normal serum potassium) are appropriate candidates for treatment with finerenone (Figure 2). In addition, finerenone may be added to a RASi alone for patients who do not tolerate or are not candidates for an SGLT2i.[163]

Practice Point 1.4.3: To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

MRA are known to increase serum potassium concentration and risk of hyperkalemia. To mitigate this risk, the FIDELIO-DKD and FIGARO-DKD trials restricted eligibility to patients with normal serum potassium concentration (after maximizing RASi) and implemented a standardized potassium-monitoring protocol. These approaches yielded acceptable rates of hyperkalemia with few attributable serious adverse events. Specifically, the FIDELIO-DKD and FIGARO-DKD trial protocols mandated a serum potassium concentration consistently ≤4.8 mmol/l during screening. While some participants had a slightly higher serum potassium of 4.9–5.0 mmol/l at randomization, selection was primarily based on a concentration ≤4.8 mmol/l, and patient selection in clinical practice should focus on patients who consistently meet this target. In the FIDELIO-DKD and FIGARO-DKD trials, serum potassium was checked 1 month after drug initiation, 4 months after drug initiation, and every 4 months thereafter. Finerenone was continued with serum potassium ≤5.5 mmol/l. With serum potassium >5.5 mmol/l, the drug was temporarily withheld and serum potassium was rechecked within 72 hours. Use of dietary potassium restriction and concomitant medications, such as diuretics and dietary potassium binders, was allowed, and the drug was reinitiated if and when potassium returned to ≤5.0 mmol/l. Clinicians should follow a similar approach to selecting and monitoring patients for nonsteroidal MRA therapy, increasing the likelihood that the acceptable adverse-event profile seen in the FIDELIO-DKD and FIGARO-DKD trials is maintained when applied to clinical practice (Figure 9).

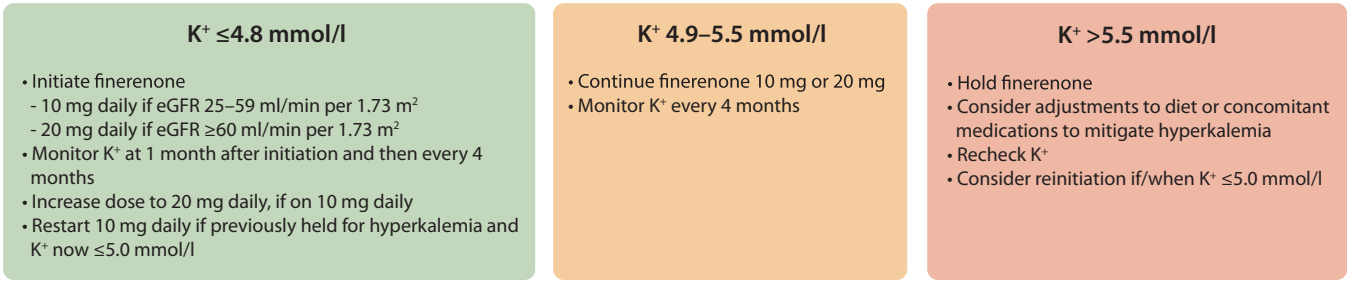


Figure 9 | Serum potassium monitoring during treatment with finerenone. Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD). 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.

Practice Point 1.4.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Currently, the only nonsteroidal MRA for which long-term clinical outcomes have been rigorously ascertained is finerenone. In the FIDELIO-DKD and FIGARO-DKD trials, finerenone was started at a dose of 20 mg daily when eGFR was ≥60 ml/min per 1.73 m^2 or at a dose of 10 mg daily when eGFR was 25–59 ml/min per 1.73 m^2, with uptitration to 20 mg daily if serum potassium remained ≤4.8 mmol/l. Steroidal MRA do not have documented clinical kidney or cardiovascular benefits, except when heart failure is present.

Practice Point 1.4.5: A steroidal MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

Steroidal MRA are standard of care for treatment of heart failure (particularly with reduced ejection fraction) and primary hyperaldosteronism.[156,157] Steroidal MRA are also useful for reducing blood pressure in the setting of refractory hypertension.[155] When a steroidal MRA is already used for one of these indications, there is no evidence that switching to a nonsteroidal MRA will improve outcome, and adding a nonsteroidal MRA is likely to increase adverse effects and should not be done. When a patient is treated with neither a steroidal MRA nor a nonsteroidal MRA but has indications for both (e.g., T2D with heart failure and albuminuria on first-line therapies), the most clinically pressing indication should drive the selection of MRA. Currently, a nonsteroidal MRA cannot be a replacement for steroidal MRA for the indications of heart failure and hyperaldosteronism.

Research recommendations

- The effect of MRA on progression of CKD and development of kidney failure, as well as CVD effects, should be examined in patients with diabetes and CKD. Evaluation should also be made regarding the deleterious effects of supramaximal doses on hyperkalemia, AKI, and hypotension.
- More data are needed on combining MRA with other effective classes of medications, including SGLT2i and GLP-1 RA.
- Trials are needed to examine the benefits and risks of MRA in additional relevant study populations, including patients with T2D and normal urine albumin excretion, patients with T1D and CKD, patients who have received a kidney transplant, patients with CKD but without T2D, and patients who are treated with dialysis.
- Studies are needed to assess the comparative effects of steroidal and nonsteroidal MRA, particularly for patients for whom both classes of medication may be indicated by virtue of multiple comorbidities (e.g., CKD and heart failure).
- Real-world data on the outcomes of nonsteroidal MRA use in clinical practice are needed to verify uptake effectiveness and safety outside of the clinical trial setting.
- Health economic evaluation should be performed on the implementation of nonsteroidal MRA.

1.5 Smoking cessation

Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products *(1D)*.

This recommendation places a high value on the well-documented health and economic benefits of avoiding tobacco products among the general population, and the absence of a strong a priori rationale for why these data would not apply to people with diabetes and CKD. The recommendation places a lower value on the lack of direct evidence for benefit in people with diabetes and CKD specifically. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. Tobacco use remains a leading cause of death across the globe and is also a known risk factor for the development of CKD.[179] Recent data also highlight the relationship of secondhand smoke with kidney disease.[180] Although no RCTs have examined the impact of smoking cessation on cardiovascular risk in those with CKD, observational studies have highlighted the harmful cardiovascular effects associated with smoking.[181] More recently, electronic nicotine delivery systems, referred to as e-cigarettes, have been reported to increase the risk of lung disease and CVD.[182] Data on e-cigarettes in those with kidney disease are sparse. Thus, given the preponderance of the evidence of tobacco cessation benefits reported in the general population, healthcare professionals should assess the use of tobacco products and counsel patients with diabetes and CKD to quit using tobacco products.

Quality of evidence. Among people with diabetes and CKD, smoking cessation interventions have been examined in only 1 small randomized crossover trial with a total of 25 participants, 10 of whom did not have diabetes and were not included in the analysis. The timeframe for this study was short: 8 hours of controlled smoking versus 8 hours of nonsmoking (in the same subjects) on separate days. The quality of the evidence from this study for surrogate outcomes was low because of very serious imprecision (only 1 study and few participants). Critical clinical outcomes, such as death, kidney failure, and cardiovascular events were not reported, and therefore the overall quality of the evidence has been rated as very low (Supplementary Table S10[183])

Values and preferences. The cardiovascular benefits of smoking cessation and the feasibility of making attempts to stop smoking were judged to be the most important aspects

to patients. The Work Group also considers it important for patients to address smoking cessation during routine clinical visits despite competing issues that have to be addressed during office visits. In the judgment of the Work Group, the well-documented clinical benefits of tobacco abstinence, and the availability of various interventions in nearly all settings, justify a strong recommendation.

Resource use and costs. Smoking cessation strategies include behavioral interventions, pharmacotherapy, and a combination thereof. Behavioral interventions include assessment of tobacco use and willingness to quit, followed by counseling during office visits. Clinicians should present available treatment options to those who use tobacco products and make recommendations based on cost, affordability, and availability. These include FDA-approved treatment options, such as nicotine replacement therapy (patch, gums, lozenges, nasal spray, and inhalers) and medications, such as bupropion and varenicline, with appropriate dose adjustments depending on the level of kidney function. In the absence of expertise in offering smoking cessation therapy, referral to trained healthcare providers should be considered.

Considerations for implementation. Assessment of tobacco use would help physicians identify high-risk individuals. The benefits of abstinence from tobacco products are not likely to differ based on sex or race. Physicians should consider affordability (when using nicotine-replacement products) and access to various resources while making treatment recommendations. Overall, these recommendations are similar to those in the KDIGO 2012 CKD guideline, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the primary prevention of CVD,[1] and the US Public Health Service's Clinical Practice Guideline for Treating Tobacco Use and Dependence, which should facilitate efforts at implementation.

Rationale

Various forms of tobacco exposure continue to contribute to excess cardiovascular and other causes of death in multiple parts of the world.[184] Population-based studies note that exposure to secondhand smoke is associated with a higher prevalence of kidney disease and the development of incident kidney disease. Although use of e-cigarettes has increased over time, their safety, especially with regard to CVD, has been questioned, and their effects on kidney disease are unknown.[185,186] Although they are not recommended as a treatment option for those with tobacco addiction, they are being used by adults who would like to quit smoking. A prospective cohort study comparing the cardiovascular risk of current or former smokers versus never smokers in diabetic patients with CKD reported a higher incidence of cardiovascular events among current or prior smokers.[187] Similar findings have also been noted in other large cohort studies wherein CKD patients who were smoking had a higher risk of cardiovascular events than did nonsmokers and former smokers. In the general population, interventions that combine pharmacotherapy and behavioral support increase smoking cessation success.[188] Although dedicated trials are lacking in those with CKD, these interventions are likely to confer similar benefits in those with diabetes and CKD.[185]

Practice Point 1.5.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Secondhand smoke exposure increases the risk of adverse cardiovascular events in the general population, and associations of such events with incidence of kidney disease have also been reported.[180] As the prevalence of smoking has decreased over time and with restrictions on using tobacco products, exposure to secondhand smoke has decreased in certain countries, although the risk persists in several other regions. Thus, while assessing the use of tobacco products, exposure to secondhand smoke should also be ascertained, and patients with significant exposure should be advised of the potential health benefits of reducing such exposure.

Research recommendation

- Further examine the safety, feasibility, and beneficial effects of various interventions (e.g., behavioral vs. pharmacotherapy) for quitting tobacco product use in clinical studies.

Chapter 2: Glycemic monitoring and targets in patients with diabetes and CKD

2.1 Glycemic monitoring

Recommendation 2.1.1: We recommend using hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD *(1C)*.

This recommendation places a higher value on the potential benefits that may accrue through accurate assessment of long-term glycemic control, which in turn may maximize the benefits and minimize the harms of glucose-lowering treatment. The recommendation places a lower value on inaccuracy of the HbA1c measurement as compared with directly measured blood glucose in advanced CKD. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. HbA1c measurement is the standard of care for long-term glycemic monitoring in T1D and T2D. Long-term glycemic monitoring allows patients to assess their diabetes control over time. Assessment of diabetes control is required to achieve glycemic targets. Glycemic targets are set to prevent diabetic complications and avoid hypoglycemia. In RCTs, targeting lower HbA1c values using glucose-lowering medications has been proven to reduce risks of microvascular diabetes complications (i.e., kidney disease, retinopathy, neuropathy) and, in some studies, also macrovascular diabetes complications (i.e., cardiovascular events).[189–193]

The National Glycated Hemoglobin Standardization Program (NGSP) established a certification process to benchmark calibration of HbA1c measurements.[194] The International Federation of Clinical Chemistry Working Group on HbA1c Standardization developed specific criteria for HbA1c analyses based upon 2 reference methods—mass spectroscopy and capillary electrophoresis with ultraviolet-visible detection. Proficiency testing data show that over 97% of assays from participating laboratories that use these methods provide results within 6% of the target values of the NGSP.[195] HbA1c is also often measured by point-of-care instruments, for which proficiency testing data are not sufficient to provide such assurance.

Glycated albumin and fructosamine have been proposed as candidates for alternative long-term glycemic monitoring. These biomarkers reflect glycemia in a briefer timeframe (2–4 weeks) than HbA1c due to their shorter survival time in blood. In observational studies, glycated albumin is associated with all-cause and cardiovascular mortality in patients treated by chronic hemodialysis.[196] However, compared with actual blood glucose, the glycated albumin assay is biased by hypoalbuminemia, a common condition in patients with CKD due to protein losses in the urine, malnutrition, or peritoneal dialysis.[197] Fructosamine may also be biased by hypoalbuminemia and other factors.

Two systematic reviews of observational studies in patients with diabetes and CKD found that HbA1c correlated moderately with measures of glucose obtained by fasting or morning blood levels, or the mean of continuous glucose monitoring (CGM), particularly among people with an eGFR $\geq$30 ml/min per 1.73 m^2. Although glycated albumin correlated with HbA1c, correlations with measures of glucose by fasting or morning blood levels or mean of CGM varied widely, from strong to no association. In most cases, correlations of glycated albumin with glycemia were worse than correlations of HbA1c with glycemia. The influence of CKD severity on the association of glycated albumin with blood glucose also varied, but most studies found no or weak correlations in patients with advanced CKD, especially those treated by dialysis. Correlations of fructosamine with HbA1c and mean blood glucose were examined in 4 observational studies.[196,198–200] Although fructosamine correlated with HbA1c in patients with CKD, correlations with mean blood glucose were indeterminate because of weak or absent correlations in advanced CKD, especially among those treated by dialysis. Correlations of directly measured glucose with all 3 glycemic biomarkers— HbA1c, glycated albumin, and fructosamine—were progressively weaker with more advanced CKD stages.

Quality of evidence. No clinical trials or eligible systematic reviews were identified for correlations of HbA1c, glycated albumin, or albumin with mean blood glucose among patients with CKD and T1D or T2D. Two systematic reviews of observational studies in patients with diabetes and CKD were undertaken, 1 for the comparison between blood glucose measures and HbA1c and 1 for the comparison between alternate biomarkers and blood glucose measures. Each review identified 13 studies, with 3 addressing both comparisons (Supplementary Tables S14[197,199–211] and S15[202,203,209,212–221]) The overall quality of the studies for this recommendation was difficult to determine due to lack of information provided from the identified studies, but it was rated as low. There was low-quality evidence from studies that

aimed to determine whether CGM would be more effective than HbA1c for glycemic monitoring in people with CKD, as it derives from observational studies. The evidence to support the use of alternative biomarkers to HbA1c is of very low quality, as it derives from observational studies with inconsistency in findings. These studies were appraised using an adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool,[222] as there is no agreed-upon tool to examine the quality of evidence from these studies.

Values and preferences. The Work Group judged that patients with T1D or T2D and CKD would consider the benefits of detecting clinically relevant hyperglycemia or overtreatment to low glycemic levels through long-term glycemic monitoring by HbA1c as critically important. The Work Group also judged that the limitations of HbA1c, including underestimation or overestimation of the actual degree of glycemic control compared to directly measured blood glucose levels, would be important to patients. In the judgment of the Work Group, most but not all patients with diabetes and CKD would choose long-term glycemic monitoring by HbA1c despite these limitations. The recommendation is strong; however, some patients may choose not to monitor by HbA1c or follow the suggested schedule of testing, especially those with advanced CKD, anemia, or treatment by red blood cell transfusions, erythropoiesis-stimulating agents, or iron supplements.

Resource use and costs. Long-term glycemic monitoring by HbA1c is relatively inexpensive and widely available. To the extent that HbA1c measurement aids in achieving diabetes control in patients with CKD, including those with kidney failure treated by dialysis or kidney transplant, this recommendation is likely cost-effective, but economic analyses have not been performed and would be influenced by testing frequency and consequent resource utilization and clinical outcomes.

Considerations for implementation. Patients with T1D or T2D and CKD likely benefit from glycemic monitoring by HbA1c. This recommendation is applicable to adults and children of all race/ethnicity groups, both sexes, and to patients with kidney failure treated by dialysis or kidney transplant.

Rationale

Hyperglycemia produces glycation of proteins and other molecular structures that eventuate in permanently glycated forms termed advanced glycation end-products.[223] HbA1c is an advanced glycation end-product of hemoglobin, a principle protein in red blood cells (Figure 10). As such, HbA1c is a long-term biomarker that reflects glycemia over the lifespan of red blood cells. Notably, CKD is associated with conditions such as inflammation, oxidative stress, and metabolic acidosis that may concurrently promote advanced glycation end-product formation in addition to hyperglycemia (Figure 10).[224] Conversely, HbA1c is lowered by shortened survival or age of erythrocytes from anemia, transfusions, and use of erythropoiesis-stimulating agents or iron-replacement therapies.[224,225] These effects are most pronounced among patients with advanced CKD, particularly those treated by dialysis. Therefore, the HbA1c measurement has low reliability due to assay biases and imprecision for reflecting ambient glycemia in advanced CKD.

HbA1c measurement is a standard of care for long-term glycemic monitoring in the general population of people with T1D or T2D, but inaccuracy of HbA1c measurement in advanced CKD reduces its reliability. However, in the judgment of the Work Group, HbA1c monitoring is prudent, and most patients would make this choice. This recommendation applies to patients who have T1D or T2D and CKD, with the caveat that reliability of HbA1c level for glycemic monitoring is low at more advanced CKD stages (Figure 11).

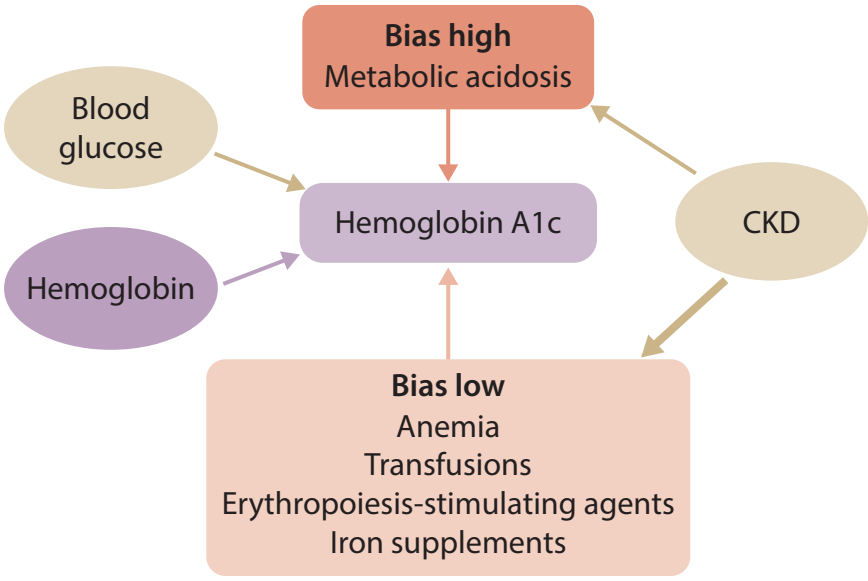


Figure 10 | Effects of chronic kidney disease (CKD)–related factors on glycated hemoglobin (HbA1c).

Population	HbA1c			GMI
	Measure	Frequency	Reliability	
CKD G1–G3b	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	High	Occasionally useful
CKD G4–G5 including treatment by dialysis or kidney transplant	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	Low	Likely useful

Figure 11 | Frequency of glycated hemoglobin (HbA1c) measurement and use of glucose management indicator (GMI) in chronic kidney disease (CKD). G1–G3b, estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2; G4–G5, eGFR <30 ml/min per 1.73 m^2.

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in glucose-lowering therapy.

HbA1c monitoring facilitates control of diabetes to achieve glycemic targets that prevent diabetic complications. In both T1D or T2D, lower achieved levels of HbA1c <7% (<53 mmol/mol) versus 8%–9% (64–75 mmol/mol) reduce risk of overall microvascular complications, including nephropathy and retinopathy, and macrovascular complications in some RCTs.[189–193] The potential harm of monitoring by HbA1c is that it may underestimate (more commonly) or overestimate (less commonly) the actual degree of glycemia control compared to directly measured blood glucose in advanced CKD. No advantages of glycated albumin or fructosamine over HbA1c are known for glycemic monitoring in CKD. Frequency of HbA1c testing is recommended as often as 4 times per year to align with a 10–12-week time period for which it reflects ambient glycemia according to normal duration of red blood cell survival. In the judgment of the Work Group, it is reasonable to test HbA1c twice per year in many patients who are stable and achieving glycemic goals. Measuring HbA1c more frequently would be reasonable in patients with adjustments in glucose-lowering medication, changes in lifestyle factors, or marked changes in measured blood glucose values, or those who are less concerned about the burden or costs of more frequent laboratory testing.[226]

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4–G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.

Correlations of directly measured blood glucose levels with 3 glycemic biomarkers—HbA1c, glycated albumin, and fructosamine—were progressively weaker with advanced CKD stages (G4–G5), especially kidney failure treated by dialysis.[196,197,205,210,227] However, HbA1c remains the glycemic biomarker of choice in advanced CKD because glycated albumin and fructosamine provide no advantages over HbA1c and have clinically relevant assay biases to the low and high levels, respectively, with hypoalbuminemia, a common condition among patients with proteinuria, malnutrition, or treated by peritoneal dialysis.[228]

Practice Point 2.1.3: A glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) data can be used to index glycemia for individuals in whom HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms.

CGM and self-monitoring of blood glucose (SMBG) yield direct measurements of interstitial and blood glucose, respectively, that are not known to be biased by CKD or its treatments, including dialysis or kidney transplant (Figure 12[229]). Therefore, if it is a clinical concern that HbA1c may be yielding biased estimates of long-term glycemia (e.g., discordant with SMBG, random blood glucose levels, or hypoglycemic or hyperglycemic symptoms), it is reasonable to use CGM to generate a glucose management indicator (GMI).[228] The GMI can be derived from CGM that is performed with results either blinded to the patients during monitoring ("professional" version) or available to the patient in real time. The GMI is a measure of average blood glucose that is calculated from CGM and expressed in the units of HbA1c (%), facilitating interpretation of the HbA1c values. For example, if HbA1c is lower than a concurrent GMI measure, the HbA1c can be interpreted to underestimate average blood glucose by the difference in measurements, allowing adjustment of HbA1c targets accordingly.[230,231] GMI may be useful for patients with advanced CKD, including those treated with dialysis, for whom reliability of HbA1c is low. It should be noted that the assay bias of HbA1c relative to GMI could potentially change over time within a patient, particularly when there are clinical changes that affect red blood cell turnover or protein glycation. In these situations, GMI needs to be re-established regularly.

Practice Point 2.1.4: Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) may help prevent hypoglycemia and improve glycemic control when glucose-lowering therapies associated with risk of hypoglycemia are used.

In addition to long-term glycemic control, minute-to-minute glycemic variability and episodes of hypoglycemia are important therapeutic targets for people with diabetes and CKD, especially those with T1D and those treated with

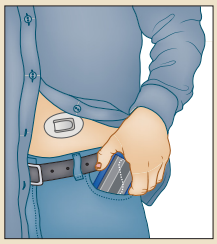
Glossary of glucose monitoring terms

Self-monitoring of blood glucose (SMBG)
Self-sampling of blood via fingerstick for capillary glucose measurement using glucometers.
Since sampling is performed intermittently, episodes of hypoglycemia or hyperglycemia are often harder to detect

Continuous glucose monitoring (CGM)
Minimally invasive subcutaneous sensors which sample interstitial glucose at regular intervals (e.g., every 5–15 min).
There are three categories of CGMs:

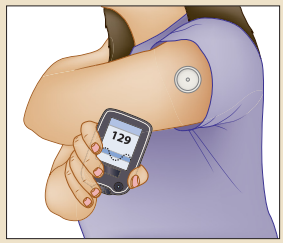
(a) Retrospective CGM
Glucose levels are not visible while the device is worn. Instead, a report is generated for evaluation after the CGM is removed

(b) Real-time CGM (rtCGM)



Refers to sensors transmitting and/or displaying the data automatically throughout the day, so that the patient can review glucose levels and adjust treatment as needed

(c) Intermittently scanned CGM

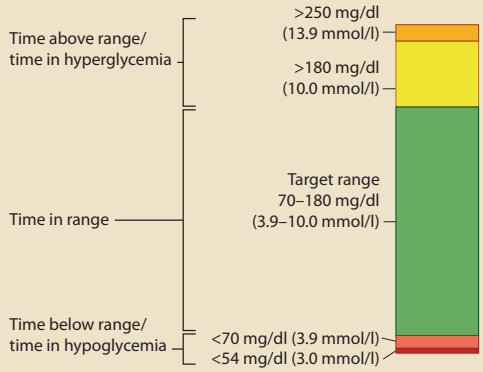


Also known as 'flash' CGM or FGM for short. Glucose levels can be seen while the device is worn when they are queried

Glucose management indicator (GMI)
Provides a measure of average blood glucose levels calculated from CGM readings, expressed in units of A1C (%), that can be used to gauge whether clinical A1C levels are falsely high or low

Time in range (TIR)
This is a metric of glycemic control that assesses the percentage of CGM readings within a certain range.

Commonly accepted ranges are 70–180 mg/dl (3.9–10.0 mmol/l) at >70% of readings; time per day



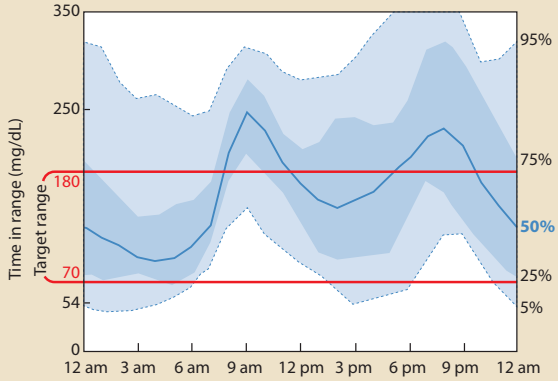


Figure 12| Glossary of glucose-monitoring terms. Adapted from American Diabetes Association, Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range, American Diabetes Association, 2019. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.[229]

hypoglycemic medications such as insulin. For daily glycemic monitoring, CGM and SMBG are frequently used but relatively high-cost options to assess real-time blood glucose. Real-time assessments of glucose promote effective self-management. Advanced CKD substantially increases the risk of hypoglycemia in patients with diabetes treated by many oral agents and insulin. Daily monitoring improves the safety of glucose-lowering therapy by identifying fluctuations in glucose as a means to avoid hypoglycemia. CGM and SMBG also aid in achieving glycemic targets. SMBG was emphasized in previous clinical practice guidelines for daily glycemic monitoring in patients with diabetes and CKD.[230,231] However, CGM was not generally available for clinical use at that time (2007), and the potential advantages of the latter may make it preferable to SMBG among patients in whom daily monitoring is desired.

In the judgment of the Work Group, there is no clear advantage of CGM or SMBG for patients with diabetes and CKD treated by oral glucose-lowering agents that do not cause hypoglycemia.[226] However, daily monitoring may mitigate the higher risk of hypoglycemia associated with taking insulin or certain oral agents (Figure 13). Although there are burdens and expenses, daily glycemic monitoring to achieve targets while avoiding hypoglycemia is prudent. In the judgment of the Work Group, many patients with diabetes and CKD would choose daily glycemic monitoring by CGM or, when CGM not readily available, SMBG, especially patients with T1D and patients using glucose-lowering therapies associated with hypoglycemia. Glucose-lowering agents not associated with hypoglycemia are preferable therapies for patients with diabetes and CKD who do not use CGM or SMBG, such as those without access to these technologies or

Antihyperglycemic agents	Risk of hypoglycemia	Rationale for CGM or SMBG
• Insulin • Sulfonylureas • Meglitinides	Higher	Higher
• Metformin • SGLT2 inhibitors • GLP-1 receptor agonists • DPP-4 inhibitors	Lower	Lower

Figure 13 | Relationship of glucose-lowering drug choice to risk of hypoglycemia and rationale for using continuous glucose monitoring (CGM) or self-monitoring of blood glucose (SMBG). DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2.

ability to do self-monitoring, or preference to avoid the daily burden.

Practice Point 2.1.5: For patients with T2D and CKD who choose not to do daily glycemic monitoring by CGM or SMBG, glucose-lowering agents that pose a lower risk of hypoglycemia are preferred and should be administered in doses that are appropriate for the level of eGFR.

Patients with diabetes and more advanced CKD stages are at increased risk of hypoglycemia. Selecting glucose-lowering agents with very low or no hypoglycemia risk should be considered, especially for patients who cannot perform or choose not to perform daily blood glucose monitoring.

Risk of hypoglycemia is high in patients with advanced CKD who are treated by glucose-lowering agents that raise blood insulin levels (exogenous insulin, sulfonylureas, meglitinides). Therefore, without daily glycemic monitoring, it is often difficult to avoid hypoglycemic episodes. This risk can be averted by using glucose-lowering agents that are not inherently associated with occurrence of hypoglycemia (metformin, SGLT2i, GLP-1 RA, dipeptidyl peptidase-4 [DPP-4] inhibitors).

Practice Point 2.1.6: CGM devices are rapidly evolving with multiple functionalities (e.g., real-time and intermittently scanned CGM). Newer CGM devices may offer advantages for certain patients, depending on their values, goals, and preferences.

CGM technology has greatly impacted diabetes self-management by providing glycemic assessment moment-to-moment, allowing patients to make real-time decisions about their hyperglycemic treatment. The technology continues to quickly develop with multiple permutations and functionalities, including real-time and intermittently scanned CGM, alarms for low and high values, direct cell phone linkage, factory calibration, new metrics such as GMI and ambulatory glucose profiles, and integration into closed-loop insulin delivery systems. Multiple devices allowing for continuous or flash glucose monitoring are now available. Consultation with a specialist in diabetes technology (certified diabetes educator or other provider) can help patients select the device that is most appropriate for patients with diabetes and CKD. Currently available devices have multiple functionalities that may include the ability to save, export, and share data to communicate with ambulatory insulin pumps directly, and to set alarms for low or high glucose levels, as well as for their rates of rise or decline. These devices differ in their accuracy, need for calibration (with fingerstick-derived blood glucose data), placement, sensor life, warm-up time, type of transmitter, display options, live data–sharing capacity, cost, and insurance coverage. Specialists in diabetes technology can assist patients with staying current with these advances and helping them choose the right CGM system for their individual needs.

Research recommendations

In patients with T1D or T2D and advanced CKD, especially kidney failure treated by dialysis or kidney transplant, research is needed to:

- Develop methods to identify patients for whom HbA1c produces a biased estimate of long-term glycemia and develop alternate approaches to monitoring glycemia in such patients.
- Develop methods to identify patients at high risk of hypoglycemia or poor glycemic control who may benefit from CGM or SMBG.
- Develop approaches to effectively apply CGM to glycemic assessment in patients at high risk of hypoglycemia or for whom HbA1c is biased.
- Determine overall benefits and harms of using SMBG and CGM.
- Develop and validate alternative biomarkers for long-term glycemic monitoring.
- Define optimal approaches for monitoring glycemia.
- Test whether CGM helps to control glycemia and improve clinical outcomes.

2.2 Glycemic targets

Recommendation 2.2.1: We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 14) *(1C)*.

This recommendation places a higher value on the potential benefits of an individualized target aimed at balancing the

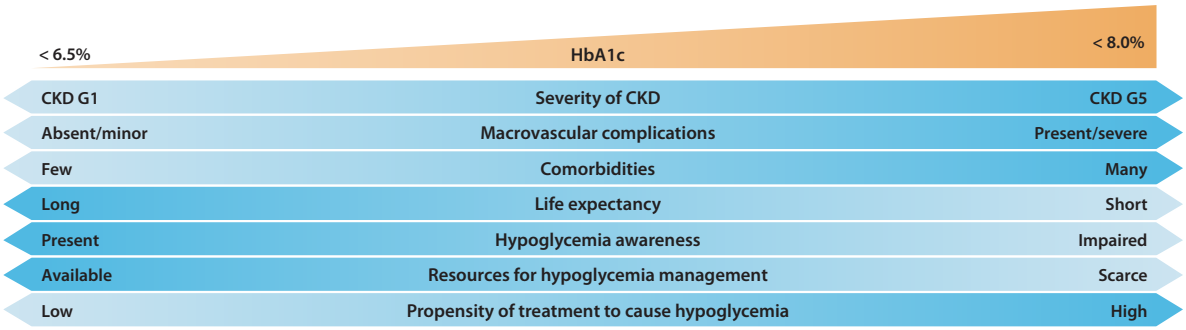


Figure 14| Factors guiding decisions on individual glycated hemoglobin (HbA1c) targets. CKD, chronic kidney disease; G1, estimated glomerular filtration rate (eGFR) ≥90 ml/min per 1.73 m^2; G5, eGFR <15 ml/min per 1.73 m^2.

long-term benefits of glycemic control with the short-term risks of hypoglycemia. The recommendation places a lower value on the simplicity of a single target that is recommended for all patients with diabetes and CKD. For patients for whom prevention of complications is the key goal, a lower HbA1c target (e.g., <6.5% or <7.0%) might be preferred. For those with multiple comorbidities or increased burden of hypoglycemia, a higher HbA1c target (e.g., <7.5% or <8.0%) might be preferred (Figure 14). This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. HbA1c targets are central to guide glucose-lowering treatment. In the general diabetes population, higher HbA1c levels have been associated with increased risk of microvascular and macrovascular complications. Moreover, in clinical trials, targeting lower HbA1c levels has reduced the rates of chronic diabetes complications in patients with T1D[190,232–238] or T2D.[239–246] The main harm associated with lower HbA1c targets is hypoglycemia. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of T2D, mortality was also higher among participants assigned to the lower HbA1c target, perhaps due to hypoglycemia and related cardiovascular events.[240]

Among patients with diabetes and CKD, a U-shaped association of HbA1c with adverse health outcomes has been observed, suggesting risks with both inadequately controlled blood glucose and excessively lowered blood glucose.[247] However, the benefits and harms for the proposed HbA1c targets on patients with T2D are derived mostly from studies that used glucose-lowering agents known to increase hypoglycemia risk. Patients randomized to lower HbA1c levels had increased rates of severe hypoglycemia in these studies. Notably, however, lower HbA1c targets may not necessarily lead to a significant increase in hypoglycemia rates when attained using medications with a lower risk of hypoglycemia.

Data from RCTs support the recommendation of targeting an individualized HbA1c level of <6.5% to <8.0% in patients with diabetes and CKD, compared with higher HbA1c targets. HbA1c targets in this range are associated with better overall survival and cardiovascular outcomes, along with decreased incidence of moderately increased albuminuria and other microvascular outcomes, such as retinopathy. HbA1c levels in this range may also be associated with lower risk of progression to advanced CKD and kidney failure.

However, the benefits of more-stringent glycemic control (i.e., lower HbA1c targets) compared with less-stringent glycemic control (i.e., higher HbA1c targets) manifest over many years of treatment.[191,248,249] In addition, more-stringent glycemic control compared with less-stringent glycemic control increases the risk of hypoglycemia.[240] Individual patient factors modify both anticipated benefits and anticipated risks of more-stringent glycemic control (Figure 14). For example, younger patients with few comorbidities, mild-to-moderate CKD, and longer life expectancy may anticipate substantial cumulative long-term benefits of stringent glycemic control and therefore prefer a lower HbA1c target. Patients who are treated with medications that do not cause substantial hypoglycemia, who have preserved hypoglycemia awareness and resources to detect and intervene early in the course of hypoglycemia, and who have demonstrated an ability to attain stringent HbA1c targets without hypoglycemia may also prefer a lower HbA1c target. Patients with opposite characteristics may prefer higher HbA1c targets. A flexible approach allows each patient to optimize these tradeoffs, whereas a "one-size-fits-all" single HbA1c target may offer insufficient long-term organ protection for some patients and place others at undue risk of hypoglycemia. Therefore, individualization of HbA1c targets in patients with diabetes and CKD should be an interactive process that includes individual assessment of risk, life expectancy, disease/therapy burden, and patient preferences.

Quality of evidence. A systematic review with 3 comparisons examining the effects of lower (≤7.0%, ≤6.5%, and ≤6.0%) versus higher (standard of care) HbA1c targets in patients with diabetes and CKD was undertaken.

The updated Cochrane systematic review[250] identified 11 studies that compared a target HbA1c <7.0% to higher HbA1c targets (standard glycemic control) (Supplementary Table S11[190,191,232,234,235,240,242–244,246,251–253]) Three studies were also identified but were not eligible for inclusion in the meta-analysis.[233,236,254] The review found that a target of

HbA1c <7.0% decreased the incidence of nonfatal myocardial infarction and onset and progression of moderately increased albuminuria, but the quality of the evidence was downgraded because of study limitations and inconsistency in effect estimates. However, there was little to no effect on other outcomes, such as all-cause mortality, cardiovascular mortality, and kidney failure.

Six studies compared a target HbA1c of ≤6.5% to higher HbA1c targets (standard glycemic control) and found that an HbA1c target of ≤6.5% probably decreased the incidence of moderately increased albuminuria, and kidney failure (Supplementary Table S12[239,240,242–244,252]) The quality of the evidence was rated as moderate for these 2 outcomes, with downgrading due to study limitations. There was little or no difference or inconclusive data on other outcomes, and the quality of the evidence was low to very low because of study limitations, heterogeneity, and serious imprecision.

Two studies comparing a target HbA1c of ≤6.0% to higher HbA1c targets (standard glycemic control) found that the lower HbA1c target probably increased all-cause mortality (Supplementary Table S13[240,242,255]) There was little or no effect on cardiovascular mortality (RR: 1.65; 95% CI: 0.99–2.75). Similarly, the lower HbA1c target of ≤6.0% decreased the incidence of nonfatal myocardial infarction and moderately increased albuminuria compared to standard glycemic control. The quality of the evidence was rated as moderate to low for these outcomes, because of study limitations, and serious imprecision.

The quality of the evidence base overall was graded as low because of either study limitations, the inconsistency of results, or imprecision. However, for onset of moderately increased albuminuria, and nonfatal myocardial infarction, the evidence quality was rated as moderate. Additionally, the majority of the evidence was extrapolated from subgroups of the RCTs in the general population of people with diabetes. However, some studies included only patients with diabetes and moderately increased albuminuria.[235,239,243] Due to indirectness, risk of bias, and heterogeneity, the quality of the evidence was rated as low.

Values and preferences. The Work Group judged that the most important outcomes for patients related to HbA1c targets are the reduced risk of microvascular and possibly macrovascular complications versus the increased burden and possible harms associated with such strategies (Figure 14). Patients with diabetes and CKD are at higher risk of hypoglycemia with traditional glucose-lowering drugs, and thus a single stringent target may not be appropriate for many patients. On the other hand, there is clear potential for more-stringent targets to improve clinically relevant outcomes (all-cause mortality, cardiovascular mortality, and progression to more advanced CKD) in certain patients. Therefore, the Work Group judged that a range of targets is more suitable than a single target for all patients. In the judgment of the Work Group, all or nearly all well-informed patients would choose an HbA1c target within the recommended range, as compared to a more-stringent or less-stringent target.

A lower HbA1c target (e.g., <6.5% or <7%) may be selected for patients for whom there are more significant concerns regarding onset and progression of moderately increased albuminuria and nonfatal myocardial infarction, and for patients who are able to achieve such targets easily and without hypoglycemia (e.g., patients treated with fewer glucose-lowering agents and with agents that are less likely to cause hypoglycemia). A higher HbA1c target (e.g., <7.5% or <8%) may be selected for patients at higher risk for hypoglycemia (e.g., those with low GFR and/or those treated with drugs associated with hypoglycemia, such as insulin or sulfonylureas). However, it is the Work Group's opinion that patients would value the use of agents with a lower risk of hypoglycemia when possible, rather than selecting a higher HbA1c target. In addition, HbA1c targets may also be relaxed (e.g., <7.5% or <8%, perhaps higher in some cases) in patients with a shorter life expectancy and multiple comorbidities. Considerations regarding life expectancy are also relevant when considering potential beneficial effects of glucose-lowering therapy. In randomized clinical trials, it has taken a number of years for benefits of intensive glycemic control to manifest as improved clinical outcomes.[190,191,234,245,246,248,256]

Resource use and costs. Lower blood glucose targets may increase costs for monitoring of blood glucose and impose an additional burden on the patient. Use of specific glucose-lowering agents, such as SGLT2i and GLP-1 RA, may have a greater impact on kidney and cardiovascular outcomes in patients with T2D and CKD than on reaching specific HbA1c targets.

Considerations for implementation. The proposed HbA1c targets are applicable to all adults and children of all races/ethnicities and both sexes and patients with kidney failure treated by kidney transplant. The suggested range for HbA1c targets does not apply to patients with kidney failure treated by dialysis; the HbA1c range in the dialysis population is unknown.

Rationale

HbA1c targets should be individualized, as benefits and harms of targeting specific HbA1c levels vary according to key patient characteristics. These include patient preferences, severity of CKD, presence of comorbidities, life expectancy, hypoglycemia burden, choice of glucose-lowering agent, available resources, and presence of a support system. RCTs in patients with diabetes (not specifically recruited with CKD) suggested that the benefits and harms are relatively balanced at the proposed individualized HbA1c targets.

HbA1c targets ≤6.0% were associated with greater risk of hypoglycemia and increased mortality in patients with T2D and increased cardiovascular risk.[240] In the judgment of the Work Group, the high rate of hypoglycemic events observed

in the lower HbA1c range may be related to the strategies used to reach these targets rather than to the targets *per se*.

Practice Point 2.2.1: Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of glucose-lowering agents that are not associated with hypoglycemia.

Glucose monitoring strategies that may aid in safe achievement of lower HbA1c targets include use of CGM[257,258] and SMBG, which are not known to be biased by CKD or its treatments, including dialysis or kidney transplant (see Section 2.1). A GMI may be generated as a proxy for long-term glycemia in conjunction with the HbA1c measurement in individual patients, allowing adjustment of glycemic goals accordingly. GMI may commonly be useful for patients with advanced CKD, including those treated with dialysis, for whom the reliability of HbA1c is low.

Practice Point 2.2.2: CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA1c for defining glycemic targets in some patients.

Although the accuracy and precision of HbA1c among patients with CKD and an eGFR ≥30 ml/min per 1.73 m^2 are similar to those in the general diabetes population, on average, HbA1c may be inaccurate for an individual patient and does not reflect glycemic variability and hypoglycemia (see above). In addition, the accuracy and precision of HbA1c are reduced among patients with CKD and an eGFR <30 ml/min per 1.73 m^2. Thus, for some patients, CGM may be used to index HbA1c by demonstrating the association between mean glucose and HbA1c (GMI) and adjust HbA1c targets accordingly, as noted above. Alternatively, CGM metrics themselves can be used to guide glucose-lowering therapy. In particular, glucose time in range (70–180 mg/dl [3.9–10.0 mmol/l]) and time in hypoglycemia (<70 mg/dl [3.9 mmol/l] and <54 mg/dl [3.0 mmol/l]) have been used as outcomes for clinical trials[259,260] and have been endorsed as appropriate metrics for clinical care.[229] To date, CGM metrics such as time in range and time in hypoglycemia have been studied most often among patients with T1D, who tend to have greater glycemic variability than patients with T2D and are at higher risk of hypoglycemia (Figure 12).

Research recommendations

- Evaluate the value of CGM and metrics such as "time in range" and mean glucose levels as alternatives to HbA1c level for adjustment of glycemic treatment and for predicting risk for long-term complications in CKD patients with diabetes.
- Establish the safety of a lower glycemic target when achieved by using glucose-lowering agents not associated with increased hypoglycemia risk.
- Establish whether a lower glycemic target is associated with slower progression of established CKD.
- Establish optimal glycemic targets in the dialysis population with diabetes.

Chapter 3: Lifestyle interventions in patients with diabetes and CKD

3.1 Nutrition intake

RCTs are the gold standard to inform medical research and guideline development. However, due to the inherently personal nature of food choice, nutrition studies are almost always observational and often retrospective. In addition, intervention studies on food intake and diet are typically hard to design as blinded studies. In general, subjects must buy and prepare their food, and be well-aware of what diet they are following. Studies in which subjects receive weighed trays can accurately assign and track diets but are unrealistic for most study designs and subject participation. Additionally, issues such as study duration and long-term follow-up, sample size, compliance, reporting issues, portion size estimation, and preparation techniques all can have dramatic effects on estimated intake.

The number of RCTs analyzing the effects of diet among people with diabetes and CKD is small. Most RCTs have a limited number of participants and/or examine short-term outcomes. Generalizing best diets for people with diabetes and CKD from such small sample sizes over a short period of time does not represent the wide body of acceptable studies, which evaluate longer periods of time with large cohorts but are not RCTs.

Application of large, multicenter studies and their results is needed in the context of diabetes, CKD, and diet. If observational data and limited clinical trial data are available for large populations, it seems reasonable to use such data. If data in the general population or the broader population of people with diabetes indicate that benefits result from certain eating patterns, in the absence of a strong rationale to the contrary, it seems reasonable to assume that these benefits will also apply to people with diabetes and CKD.

Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.

People with diabetes and CKD, as compared with the general population, are often asked to follow more intricate nutrient intake recommendations. Indeed, the complexity of creating a diet that addresses the needs of both diabetes and kidney disease may overwhelm the most dedicated patient. In this context, it is important to emphasize the primary importance of maintaining a balanced diet of healthy foods. A focus on vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts is common to many diets associated with good health outcomes in the general population. It is an appropriate starting point for patients with diabetes and CKD. In the general population, and in the nondiabetic CKD and kidney-failure population, adherence to healthy eating practices has been shown to offer numerous health benefits.[261] The benefit of consuming fewer refined and processed foods in the general population is well-established, and hence its applicability to those with diabetes and CKD is also reasonable. In advanced CKD, potassium may need to be restricted, and people may be advised to eat lower-potassium fruits and vegetables, and other foods. Inclusion of fruits and vegetables should be in line with normal diabetic diet recommendations.

Nutrition therapy can decrease HbA1c levels to levels similar to, or better than, those obtained with glucose-lowering medications. Simple advice such as increasing intake of nonstarchy vegetables, decreasing intake of added sugars and refined grains, and increasing intake of whole foods over highly processed foods can be implemented for most people across wide geographic and economic strata (Figure 15).

Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis *(2C)*.

The WHO recommends a daily protein intake of 0.8 g/kg for healthy people. In the judgment of the Work Group, this recommendation is reasonable in those with diabetes and CKD. Neither lower nor higher protein intake appears beneficial, and each is associated with potential harms. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. Compared with a standard dietary protein intake of 0.8 g/kg/d, lower dietary protein intake has been hypothesized to reduce glomerular hyperfiltration and slow progression of CKD.[262] However, limiting protein intake to less than 0.8 g/kg/d in a person with diabetes, who also may have been counseled to limit carbohydrates, fat, and alcohol, may dramatically decrease caloric content of the diet. Such dramatically restrictive diets will, if followed, lead to significant weight loss, which may or may not be desirable, and will probably result in a decrease in

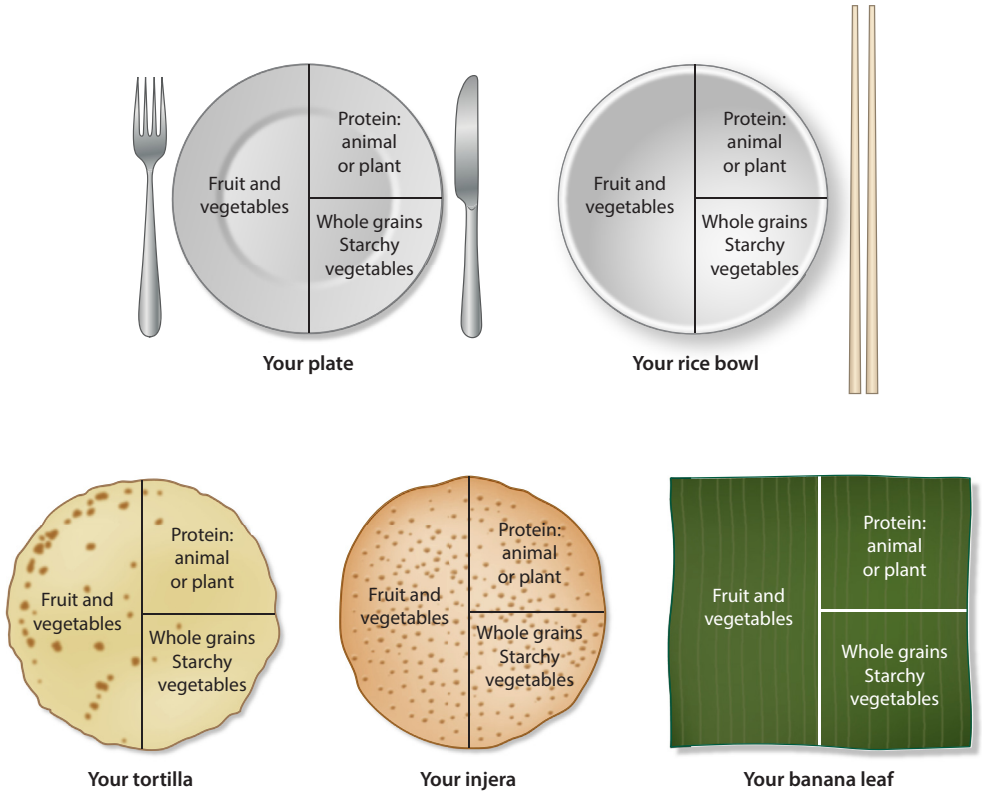


Figure 15 | What does a healthy kidney diet look like?

quality of life for those attempting such limitations. In countries or individuals with relatively low protein intakes, the possibility of malnutrition from protein and calorie deficit is possible. Patients with advanced CKD may naturally decrease their oral intake, leading to malnutrition. It may be desirable to increase protein intake recommendations in certain individuals. Additionally, protein intake on a diabetic diet is especially crucial to avoid episodes of hypoglycemia; limiting it in the diet may make such potentially dangerous episodes more common.

Some diets advocate protein intake greater than 0.8 g/kg/d, especially to reduce carbohydrate intake or promote weight loss. However, long-term effects of high-protein diets (especially >1.0 g/kg/d) on kidney function are not known and could potentially cause harm by requiring increased kidney excretion of amino acids.[263] A high protein intake could also increase acid load and precipitate or worsen metabolic acidosis, particularly in those with lower levels of kidney function. Dietary recommendations should take into account individual nutrition needs such as age, weight, physical activity, and comorbidities, including for those patients who may need a higher protein diet at early stages to allow for a reduction of carbohydrates to better manage their diabetes.

Quality of evidence. The overall quality of the evidence is low. In addition to the concerns about bias exhibited in these trials (i.e., study limitations, imprecision, and inconsistency), the evidence is indirect, as it is derived from general diabetes and general CKD population trials.

This recommendation is based upon the WHO recommendation for protein intake for the general population.[263] A Cochrane systematic review on a very low–protein diet (0.3–0.4 g/kg/d) compared to a low-protein diet (0.5–0.6 g/kg/d) or normal-protein diet (≥0.8 g/kg/d) for 12 months found that it likely had little or no effect on death and/or kidney failure (moderate-quality evidence). The quality of the evidence was downgraded because of imprecision and inconsistency.[264] The question whether to use a very low–protein diet combined with keto acids in diabetes was not included in the original literature review.

Despite the high burden of diabetes and CKD, few studies have examined the clinical impact of diet modification in this patient population. An exhaustive literature search failed to show more than weak to very weak evidence that limiting protein intake to less than normal recommendations slowed the progression of kidney failure or decreased mortality.

A systematic review of the literature found 11 studies on protein restriction for inclusion, but results were inconclusive, had little to no effect on HbA1c, or did not look at cardiovascular events or progression to kidney failure (Supplementary Table S16[265–276]). A systematic review of all study types, including observational studies examining harms caused by high-protein diets was conducted, and 1127 citations were identified. The review found no relevant studies, no long-term studies, and inconclusive evidence.

Values and preferences. Lists of food to be included or excluded from patients' diets frequently do not consider the

individual patient's income, cooking abilities, cultural preferences, food availability, or practicality. In addition, patients with diabetes and CKD often have multiple comorbid diseases, such as hypertension, gout, gastropathy, mineral–bone disorders, and/or cardiac disease, which may further complicate an already complex diet regimen. Income, food insecurity, ability to cook and prepare food, dentition, and family food needs may also impact a patient's ability to maintain the recommended diet. Limiting or eliminating foods with important cultural significance can be deeply painful to patients. However, when a patient-centered care discussion can occur, many individuals may willingly trade the moderation of their oral intake for the ability to avoid costly medications or unwanted side effects. In order to follow this type of nutrition therapy, patients must learn and apply new nutrition-related behaviors. People facing more progressive CKD and kidney failure in particular may be highly motivated to implement nutrition solutions to address their diagnosis.

This recommendation places a relatively higher value on evidence and recommendations from the general population, suggesting that protein intake of 0.8 g/kg/d is associated with good outcomes.[263] The recommendation places a relatively lower value on the impact of these dietary changes on quality of life, and on the possibility that data from the general population will not apply to people with diabetes and CKD. In the judgment of the Work Group, people who are willing and able to make the required modifications to their diet and who are interested in the possibility of a benefit will be inclined to follow this recommendation. In contrast, people who are less willing or able to modify their diet for the reasons given above will be less inclined to follow the recommendation.

Resource use and costs. Patients often would like to participate in determining what nutrition alterations are reasonable and available to them, and which are not. Families must play a role in deciding how scarce resources will be distributed within family units. Recommendations that could increase intake of expensive or unobtainable foods may limit a patient's ability to provide adequate nutrition to the rest of their family. Recommendations and problem-solving with the patient who considers these things may provide them with less expensive, healthier meals, contributing to their health and well-being, as well as that of their families.

Although most people with diabetes do not receive nutrition education, many people may see nutrition interventions as the least expensive and most practical way to decrease symptoms. In many situations, diet modification would lower the use of expensive medications and medical interventions as HbA1c reductions from nutrition therapy can be similar to or better than what is expected using currently available medications for T2D.

Considerations for implementation. This recommendation applies to both T1D and T2D, as well as kidney transplant recipients, but not to dialysis patients (see Practice Point 3.1.2). Patients with newly diagnosed diabetes should be referred for individualized nutrition education at diagnosis. Patients with longstanding diabetes and CKD should have access to nutrition education yearly, as well as at critical times to help build self-management skills.[277]

Although most patients would be amenable to lifestyle modifications, some may be unwilling or unable to implement these and will need alternative options and substitutions that warrant discussions with them. These include referral to peer-counseling programs, village health workers, registered dietitians, accredited nutrition providers, or diabetes education programs. Those with rapid decline in kidney function especially would warrant referral to nutrition healthcare team members.

A table of protein guidelines based on 0.8 g protein/kg for adults with diabetes and CKD not requiring dialysis is found in Figure 16, showing the amount of protein in grams based on body weight. In patients who are significantly overweight, protein needs should be calculated by normalizing weight to the median weight for height.[263] Alternatively, in overweight patients, clinicians may use an ideal weight to multiply by 0.8 g protein/kg/d, rather than the patient's actual weight, to avoid excessively high protein intake estimation. There is no evidence to suggest that this recommendation should vary based on patient age or sex. Clinicians should advise patients not to confuse grams of protein per day with the weight of food in grams (i.e., 100 g of meat contains only about 25 g of protein; Figure 17).

Rationale

High-protein intake contributes to the development of increased intraglomerular pressure and glomerular hyperfiltration, which in turn leads to glomerulosclerosis and tubulointerstitial injury.[278] Experimental models and studies in humans showed improvement in kidney function with protein restriction. In few clinical studies, predominantly enrolling those with nondiabetic and especially advanced CKD, a low-protein intake (compared to those with normal-protein intake of 0.8 g/kg/d) has been demonstrated to slow down the decline in kidney function.[264] However, clinical trials comparing different levels of protein intake are lacking

Weight (kg)	35	40	50	55	60	65	70	75	80	85	90	95	100
Grams of protein per day (wt × 0.8 g/kg)	28	32	40	44	48	52	56	60	64	68	72	76	80

Figure 16 | Protein guideline for adults with diabetes and chronic kidney disease (CKD) not treated with dialysis. wt, weight.

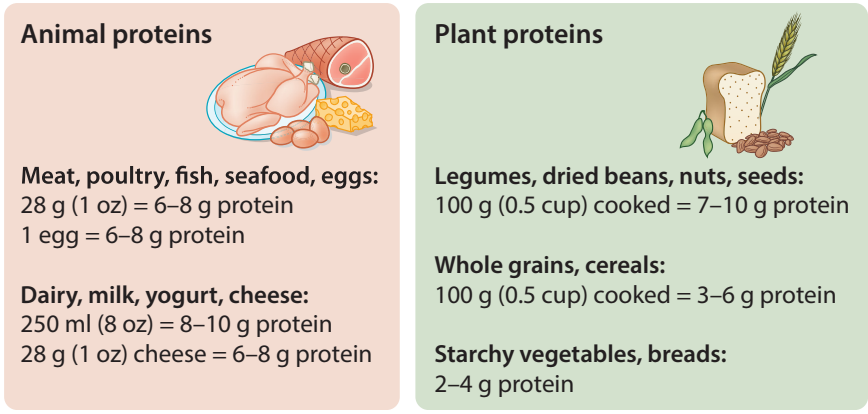


Figure 17 | Average protein content of foods in grams.

in those with diabetes and CKD, and thus the Work Group extrapolated data from recommendations of the WHO for protein intake for the general population.[263]

The Work Group also considered the potential harmful impact of very low–protein intake (0.4–0.6 g/kg/d), which could lead to malnutrition in those with CKD. In addition, differences in both amount and type of protein intake (animal vs. vegetable), affordability, availability, and cultural factors across various countries were considered.[279] Although observational studies have reported that high consumption of red and processed meat is associated with increased risk of CKD progression and mortality, fruit and vegetable intake were associated with decline in progression of kidney disease.[280–282] Given that these benefits have not been corroborated in clinical trials, the Work Group did not make any specific recommendations for the type of protein intake in those with diabetes and CKD. Also, no existing evidence supports different recommendations based on the severity of kidney disease. Thus, the current recommendation applies to all in the CKD population not treated with dialysis, and Practice Point 3.1.2 provides guidance for those on dialysis. Overall, these recommendations are also similar to the KDIGO 2012 CKD guideline and the Kidney Disease Outcomes Quality Initiative (KDOQI) 2020 nutrition guidelines.[283,284]

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Dialysis has long been known to cause a catabolic response. Amino acid losses during both hemodialysis, and particularly peritoneal dialysis, are well-documented. Uremia itself causes depressed appetite, increased catabolism, and decreased muscle mass.[285] Recommendations for these patients are based on nitrogen balance studies, presence of uremia, and malnutrition.[286] Additionally, a slightly higher protein intake in patients with diabetes treated with dialysis may help avoid hypoglycemia, given their decreased ability for gluconeogenesis. This practice point mirrors guidance from the KDOQI 2020 nutrition guidelines.[284]

Recommendation 3.1.2: 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 patients with diabetes and CKD *(2C)*.

This recommendation places a relatively high value on the potential benefit of reducing dietary sodium to 2 g of sodium per day (90 mmol of sodium per day or 5 g of sodium chloride per day) in improving blood pressure and is associated with lower cardiovascular risk for the general population.[287] The recommendation places a relatively lower value on the impact of these dietary changes on quality of life, and on theoretical concerns that these benefits will not extend to people with diabetes and CKD, for example, because of impaired urinary sodium excretion. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. High sodium intake raises blood pressure and increases the risk of stroke, CVD, and overall mortality. In the general population, sodium reduction alone or as part of other diets such as the Dietary Approaches to Stop Hypertension (DASH) diet, rich in fruits, vegetables, and low-fat dairy products, lowers blood pressure.[287,288] Population-based studies have reported that sodium consumption above a reference level of 2 g/d contributed to over 1.65 million deaths from cardiovascular causes in 2010 alone. In those with kidney disease, low sodium intake also augments the benefits of RAS blockers.

The US National Academy of Sciences group found that there was "insufficient and inconsistent evidence of harmful effects of low sodium intake on type 2 diabetes, glucose tolerance, and insulin sensitivity." It concluded that limiting sodium intake to 1.5–2.3 g/d was not linked to any harm, finding "insufficient evidence of adverse health effects at low levels of intake."[289]

People with orthostatic hypotension may need their sodium intake to be guided by their healthcare provider, just as in some rare cases with excessive sweat sodium losses during

high temperatures and high levels of physical activity. Individuals in countries where iodized salt is the main source of iodine, whose fortification level assumes a daily intake of >5 g sodium per day, may need to discuss their salt intake with their treating physician, specifically.

Quality of evidence. The overall quality of the evidence was rated as low because of a reliance on indirect studies from the general diabetes population that exhibit moderate quality of the evidence for important clinical outcomes.

Fifteen relevant studies were identified comparing low-salt versus normal-salt diets in several groups (Supplementary Tables S17–S20[290–305]). All studies contained small numbers of patients and examined surrogate outcomes, with the quality of the evidence being low due to risk of bias and inconsistency or imprecision. "Long-term" studies had a mean follow-up of 5 weeks, and "short-term" studies had a mean follow-up of 6 days.

Almost all studies investigating nutrition interventions in kidney disease stem from epidemiologic and/or small retrospective studies, and these studies are generally rated as having low quality of evidence because of their inherent bias by design. Very few RCTs have looked at modification of diet in those with diabetes and CKD. Indeed, patients with diabetes or CKD are often excluded from such studies. Nutrition changes and modifications to intake typically take long periods to effect change and require months and years to yield results. Often, due to financial constraints, studies are limited to time periods too short to show any definitive changes. Additionally, patients with chronic disease, required to follow a complex diet for the rest of their lives, may often regress into old habits after extended periods of time, without repeated support and intervention.

The US Agency of Healthcare Research and Quality systematic review recently determined that in the general population, the strength of evidence for a causal relationship with reductions in sodium intake was moderate for all-cause mortality and CVD, and high for systolic blood pressure and diastolic blood pressure.[283,289] The data were insufficient for cardiovascular mortality and kidney disease. There is moderate to high quality of evidence for both a causal relationship and an intake–response relationship between sodium and several interrelated chronic disease indicators: CVD, hypertension, systolic blood pressure, and diastolic blood pressure (Figure 18).[306]

Values and preferences. Limiting sodium intake may affect the palatability of food and the perishability or shelf life of food. In people whose sodium intake is high, a change to a lower-sodium diet may require limiting their favorite foods. Individuals may, however, be willing to substitute culturally acceptable lower-sodium alternatives to favorite foods, limit their use of packaged/pre-prepared foods, and avoid eating out as often in order to decrease or avoid the use of costly medications with unwanted side effects, or if they have the ability, to decrease their blood pressure or the risk of other unwanted outcomes. It is possible to decrease a person's taste threshold for sodium in about 4–6 weeks, as the taste for salty foods is learned, not inherent.

Some individuals may not have adequate income, cooking ability, or dentition, or may experience food insecurity causing them to be unsuccessful at such restrictions. Limiting or eliminating foods with important cultural significance can be deeply distressful to patients and may affect the entire family's intake. Discussion with patients and their families focusing on real, practical changes may enable patients to

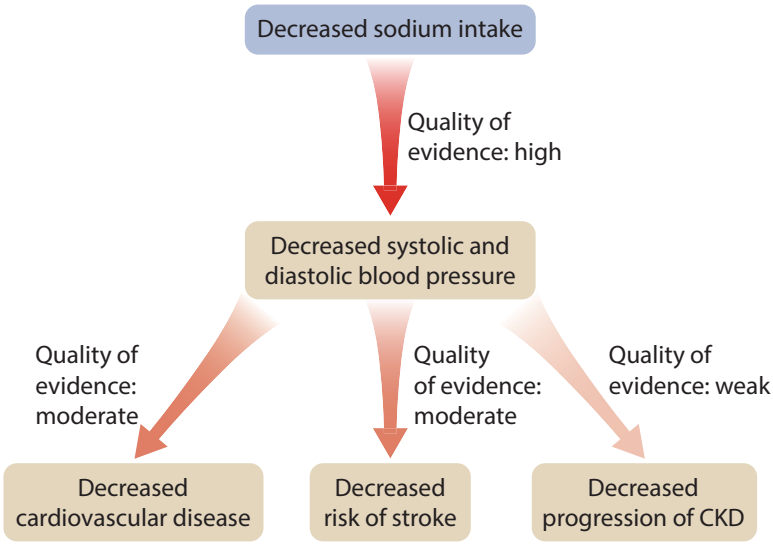


Figure 18| Effects of decreased sodium intake on various outcomes and accompanying quality of evidence.[306] CKD, chronic kidney disease.

choose a nutritional therapy that is successful for them. Many individuals may willingly trade moderating their oral intake for the ability to avoid costly medications or unwanted side effects. However, some people will be unwilling or unable to make these changes and will need other solutions.

Resource use and costs. Implementation of these recommendations for people with diabetes and CKD is feasible, even in countries with limited resources, and should be potentially cost-effective, possibly delaying or postponing the need for medications or more complex and costly kidney replacement therapies such as dialysis and/or transplant, leading to healthcare savings. Involvement and collaboration with local governmental agencies and their policies on reimbursement structures and resources should also be considered.

Strong evidence supports the medical efficacy and cost-effectiveness of nutrition therapy as a component of quality diabetes care, including its integration into the medical management of diabetes.

Considerations for implementation. Use of culturally appropriate food and incorporating a whole-foods diet philosophy may help to break the cycle of adaptation of a highly processed diet to one that is more culturally appropriate, based on use of local ingredients, enabling patients and their families to avoid financial burden and the added financial cost of medications or kidney replacement therapy (Figure 19). However, certain strategies may require tailoring. For example, the DASH-type diet or use of salt substitutes, which are rich in potassium, may not be appropriate for patients with advanced CKD. There is no evidence to suggest that this recommendation should vary based on patient age or sex.

Rationale

Low sodium intake reduces blood pressure and is associated with improved cardiovascular outcomes in those with and without kidney disease. Patients with CKD are often salt-sensitive and unable to regulate blood pressure and extracellular fluid volume status in the setting of high salt intake. Thus, patients with diabetes and CKD could benefit from restricting dietary salt intake. Further, lowering dietary salt improves volume status of the patient along with reducing proteinuria.[307] Clinical studies have also demonstrated that dietary sodium restriction might augment the effects of diuretics and RAS blockade in patients with kidney disease. Thus, despite the lack of dedicated clinical trials in those with diabetes and kidney disease, the Work Group judged that most well-informed patients would choose to restrict sodium intake to <2 g/d. Patients who are more interested in a small reduction in blood pressure and/or a lower number of antihypertensive medications (potentially reducing costs and the risk of side effects) will be more inclined to follow this recommendation. Those who are less interested in these potential benefits may have more difficulty in making the requisite dietary changes, and those who find food markedly less palatable after sodium restriction may be less inclined to follow the recommendation.

The Work Group also considered the potential impact of restricting sodium intake across various countries. The Global Burden of Disease Study examined the health effects of a high-sodium diet in 195 countries from 1990 to 2017 and estimated that a high intake of sodium caused 3 million deaths and 70 million disability-adjusted life-years. A low intake of whole grains caused 3 million deaths and 82 million

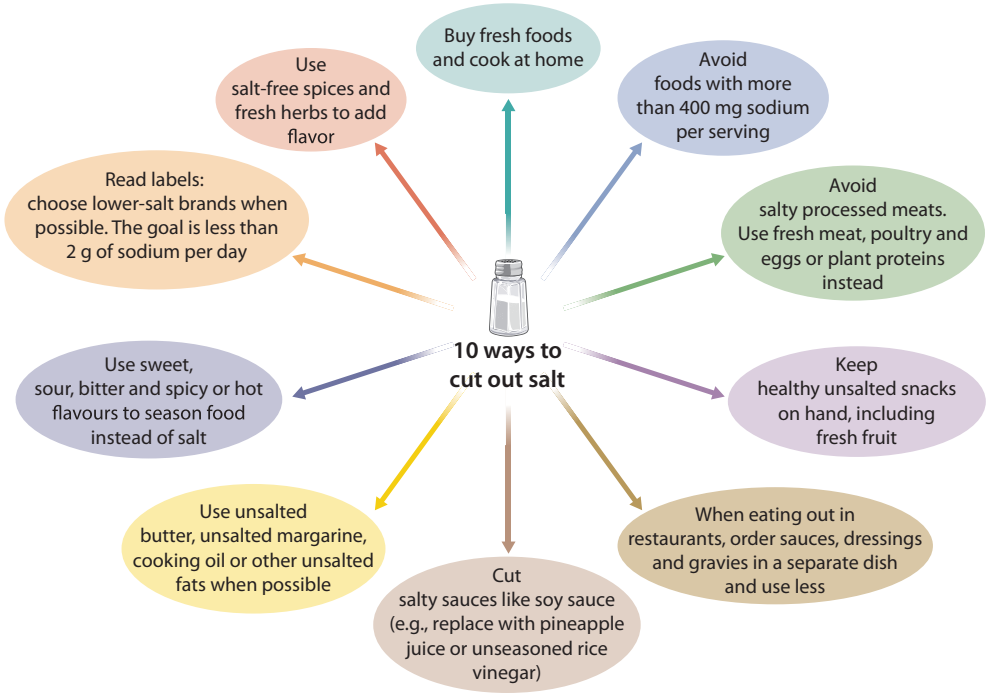


Figure 19 | Ten ways to cut out salt.

disability-adjusted life-years. A low intake of fruits caused 2 million deaths and 65 million disability-adjusted life-years.[287,306] This analysis noted that those risks held true regardless of the socioeconomic level of most nations, suggesting that benefits are likely not to vary based on the geographic location. With decline in kidney function, volume overload is common, and hence, the recommendation can be applied to all severities of kidney disease.

The US National Academy of Sciences, Engineering, and Medicine recently released *Dietary Reference Intakes for Sodium and Potassium,*[289] which indicates at least moderate strength of evidence for both causal and intake–response relationships. "Using the lowest levels of sodium intake from RCTs and evidence from the best-designed balance study conducted among adults, which used neutral balance with heat stress at 1525 mg/day, as well as utilizing data from the DASH Sodium Trial and eight other RCTs, assessment was made that the sodium recommendations were congruent and appropriate to recommend 1500 mg/day for all age groups 14 and over. For those with intakes above 2300 mg, the recommendation is to decrease intake." Larger effects in blood pressure reduction were seen in people with hypertension, but the benefits of sodium reduction were deemed to be applicable to both normotensive and hypertensive people. In agreement with the WHO, the Work Group judged that sodium intake should be restricted to <2 g/d, which although above 1.5 g/d, is less than 2.3 g/d and much less than the average intake (4–5 g/d).[308]

Practice Point 3.1.3: Shared decision-making should be a cornerstone of patient-centered nutrition management in patients with diabetes and CKD.

Modifying dietary intake is a long and complex process. Patients with diabetes and CKD often have other chronic comorbidities. Nutrition therapies may need to be coordinated to allow for patient-centered solutions, including recognition of differences in individuals such as age, dentition, cultural food preferences, finances, and patient goals, and to help align their often-conflicting comorbid nutrition requirements.

Application of patient-centered care models has shown increased adherence and increased quality of life for participants. Particularly in areas of diabetic self-management, and nutrition therapy, when patients are able to give input and offer their own solutions, outcomes are more positive for both patient and provider.[309] Patient-centered care models include patient problem-solving, allowing patients to select strategies they feel will be successful for them, supporting patients as they work through issues, supporting self-efficacy and self-confidence, and incorporating self-selected behavioral goal setting. A recognition that behavior change takes 2–8 months and that patients will fail many times before they succeed is part of the process. Involvement and education of the patients' families and/or caregivers are also highly desirable. Care must be collaborative, involving all providers, including the primary care provider, and allow for informed decision-making by patients and often their families.

Practice Point 3.1.4: Accredited nutrition providers, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the multidisciplinary nutrition care of patients with diabetes and CKD.

Recognizing that changing dietary habits and intake is a long and complex process, patients need repeated access to healthcare providers who can provide information, based on the best adult education techniques available. This access will allow patients to make informed decisions about their nutritional intake, using shared decision-making techniques. It is quite possible that the physician in these situations has neither the time, nor the expertise, to help with detailed repeated modification of the patient's diet. These interactions often require complex reporting techniques by the patient, at least an estimated nutritional analysis by the provider, and proposed options, which the patient will need to try and then accept or discard. After trial, the patient must be able to return and discuss other options if the original strategies were not satisfactory. In more sophisticated healthcare systems with accredited providers, these should be the first point of reference. In these cases, referral to a diabetes educator, registered dietician nutritionist, international nutrition-credentialed professional, or community health nurse would be desirable.

As healthcare systems vary around the world, in areas where accredited nutrition providers are scarce or nonexistent, effort should be placed on increasing the number of cost-effective peer coaches or community healthcare workers to help educate and support patients who need ongoing care coordination and culturally appropriate care. Patients who have decreased health literacy will require more time spent in an education session with healthcare providers, be they village healthcare workers, telehealth providers, physicians, nurses, international nutrition-credentialed professionals, or registered dietitian nutritionists.

In situations in which such nutrition education professionals are unavailable or unaffordable, other modes of patient support should be investigated. Peer counselors, village, or community healthcare workers trained to identify appropriate healthy alternatives, telemedicine systems, or mobile phone applications can be valuable contributors to the care of patients with diabetes and CKD, particularly in underserved areas.

When possible, technology can be used to enhance the patient's ability to learn and utilize information. Increased availability of nutrition applications for use on mobile devices, the use of social media, and more readily available nutrient database information, along with education about how to access and utilize these technologies, will help empower patients.

Practice Point 3.1.5: Healthcare providers should consider cultural differences, food intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to patients and their families.

Giving up foods that bring pleasure is a difficult and often painful adjustment. Patient preferences may allow for acceptable alternatives that exist nationally and within the local context of eating, which would be very acceptable to patients if they were informed of them. Information should be accessible to care providers and patients about the nutritional content of the foods they eat. Providers should have knowledge of acceptable alternatives, methods of preparation, and the costs of alternative recommendations. With adaptability and flexibility, almost all foods can be worked into a diet pattern for individual patients. People will experience an improved quality of life when they can incorporate foods they enjoy into their diet and still have healthy outcomes.

Many locally grown and home-prepared foods are less expensive and higher in nutrient content and are acceptable alternatives for patients. Being knowledgeable about local ways of eating, nutritional content of local foods, and acceptable alternatives can decrease the cost of following a special diet, make eating a pleasure, and allow patients to be adherent without an undue burden. Managed well, a diet for patients may translate into lower cost, as well as healthier eating for their families, who are at higher risk of kidney disease.

Research recommendations

- The potential for nutritional studies to decrease the cost and scope of other much more intrusive interventions should not be discounted. Thus, cost-effectiveness studies that demonstrate whether a preventative approach to diabetes and CKD can decrease cost of therapy for both diseases are needed.
- Investigate how different techniques of nutrition education and dietary modification such as shared decision-making, behavior-modification techniques, and motivational interviewing, can affect patient-reported outcomes, including quality of life.
- Compare the benefits and harms of plant-based versus animal-based protein in those with diabetes and CKD.
- Investigate the use of ideal body weight versus adjusted body weight in calculation of protein needs in obese patients.
- Investigate the use of village healthcare workers, peer counselors, and other nontraditional healthcare workers in situations in which utilization of more traditional healthcare positions is not possible.
- Investigate the use of technology-based interventions to develop a personalized dietary approach and test their efficacy in patients living in rural areas.
- The benefit of sodium restriction is largely derived from observational studies in the general population. Observational studies in heart failure and T1D with CKD[310] have suggested that salt restriction is not necessarily beneficial, possibly because of concomitant medication including RAS blockade and diuretics. Thus, a long-term study looking at the interaction between sodium restriction and medication in diabetes and CKD is warranted.

3.2 Physical activity

Recommendation 3.2.1: We recommend that patients with diabetes and 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)*.

This recommendation places a high value on the well-documented health and economic benefits of regular physical activity, among the general population, and the absence of data or a strong rationale for why these data would not apply to people with diabetes and CKD. The recommendation places a lower value on the lack of direct evidence for benefit in people with diabetes and CKD specifically. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. The various health benefits of engaging in regular physical activity are well-known.[1,311] Patients with diabetes and CKD have lower levels of physical activity, along with reduced overall fitness levels, as compared to the general population.[312] In fact, over two-thirds of adults with CKD in the US do not meet the physical activity levels recommended by the AHA and the American College of Sports Medicine.[312,313] In both the general population and those with CKD, lower levels of physical activity and physical fitness are associated with progressively higher risks of ASCVD and mortality.[314,315] Despite these known associations, very few clinical trials have examined the impact of different exercise programs and implementation of routine physical activity in people with diabetes and CKD.[311,316,317] In the general population and those with diabetes, improvement in physical activity levels offers cardiometabolic, kidney, and cognitive benefits.[1,311,318] Further, evidence suggests better overall well-being and quality of life among those engaging in regular physical activity, along with a dose-dependent effect. Similar benefits are anticipated in those with diabetes and CKD who engage in physical activity regularly.[319] However, CKD patients are often older and are at increased risk of falls.[320] They also have functional limitations, which might preclude participating in regular exercise and high-intensity activities.[321,322] Despite some limitations, the overall evidence points to encouraging patients to participate in daily moderate-intensity physical activity along with participating in structured programs based on access to these resources, which would offer both cardiovascular and kidney benefits.[323]

Quality of evidence. Evidence supporting physical activity in people with CKD stems from epidemiologic and/or small single-center prospective studies. Very few clinical trials have examined the impact of supervised exercise training on kidney disease progression and CVD in people with CKD.[324]

RCTs that have examined exercise interventions in patients with diabetes and CKD have been of insufficient duration to examine critical clinical outcomes such as death, kidney failure, and cardiovascular events, and have mainly reported surrogate clinical outcomes. The quality of the evidence for RCTs comparing aerobic and resistance training interventions in combination with diet, versus with diet alone, was low because of study limitations (unclear blinding of outcome assessors) and imprecision (only 1 study; Supplementary Tables S21 and S22[325,326]) One trial compared aerobic exercise along with standard of care to standard of care/medical management only. The quality of the evidence was low due to study limitations (unclear blinding of participants/investigators and outcome assessors) and imprecision (only 1 study) for critical outcomes and blood pressure. The quality of evidence was also very low for kidney function outcomes because of risk of bias and very serious imprecision (only 1 study had very wide confidence intervals indicating appreciable benefit and harm) (Supplementary Tables S21 and S22[325,326]) The evidence that supports these clinical recommendations is indirect as it is mostly based on systematic reviews of RCTs that included people both with and without diabetes, and with and without CKD,[325] and hence the overall quality of the evidence was very low.

Values and preferences. The effects of higher levels of physical activity on overall cardiovascular and kidney health, health-related quality of life, and the feasibility of engaging in regular activity were judged to be the most important aspects to patients. The Work Group also judged that recommending physical activity to patients during routine clinical visits despite competing issues that must be addressed during office visits would be important to patients. In the judgment of the Work Group, the well-documented clinical and economic benefits of physical activity, as well as the relative lack of specific resources required to implement the intervention, and the availability of the intervention in nearly all settings, all justify a strong recommendation.

Resource use and costs. Implementation of interventions to improve physical activity (such as walking, running, biking, etc.) is feasible even in countries with limited resources and is potentially cost-effective.[327] In high-income countries, engaging in structured exercise programs such as aerobic and resistance training might be feasible and can be adopted based on availability and affordability.

Considerations for implementation. Assessment of baseline physical activity levels and their physical tolerance would help physicians identify high-risk populations and seek assistance from other healthcare team members (exercise therapists, other specialists, etc.) to provide appropriate guidance to high-risk patients. Patients with diabetes and CKD who are at higher risk of adverse events (such as falls during vigorous physical activity) and those with pre-existing CVD should consult their healthcare providers before engaging in high-intensity activities. Benefits of engaging in routine physical activity are similar among men and women and are unlikely to differ based on race or ethnicity. Overall, these recommendations are similar to the KDIGO 2012 CKD guidelines[283] and the recently released ACC/AHA guidelines on the primary prevention of CVD,[1] which should facilitate efforts at implementation.

Rationale

Physical activity defined as bodily movement produced by the skeletal muscle requires energy expenditure and is usually performed throughout the day. Depending on the energy expenditure, physical activity is classified into light-, moderate-, and vigorous-intensity activities (Figure 20[313]).

Data from the WHO indicate that the global age-standardized prevalence of insufficient physical activity was 27.5%, and the 2025 global physical activity target (a 10% relative reduction in insufficient physical activity) will not be met based on the current trends of physical activity, thus

Intensity of physical activity	METS	Examples
Sedentary	< 1.5	Sitting, watching television, reclining
Light	1.6–2.9	Slow walking, household work such as cooking, cleaning
Moderate	3.0–5.9	Brisk walking, biking, yoga, swimming
Vigorous	> 6	Running, biking, swimming, lifting heavy weights

Figure 20 | Examples of various levels of physical activity and their associated metabolic equivalents (METs). A MET is a unit useful for describing the energy expenditure of a specific activity. A MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest. Republished with permission of the American Society of Nephrology, *Clinical Journal of the American Society of Nephrology*, Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. Beddhu S, Wei G, Marcus RL, et al., volume 10, issue 7, 2015, permission conveyed through the Copyright Clearance Center, Inc.[313] Copyright © American Society of Nephrology.

arguing for efforts to address this issue across the world.[328] Patients with diabetes and CKD often have other chronic comorbidities, including obesity, that contribute to the higher risk of CVD and kidney disease progression. Further, loss of muscle mass and development of complications such as anemia might limit the functional capacity of these patients as kidney function continues to decline.[321] Notably, over two-thirds of adults with CKD do not meet the minimum recommended goal of physical activity (450–750 metabolic equivalents [METs]/min/wk) (Figure 21).[312,313] This situation worsens as kidney function declines, which *per se* leads to reduced functional capacity. To further complicate this, sedentary behavior is common in CKD with over two-thirds of daylight time spent being sedentary (approximately 40 min/h).[313] Sedentary behavior is defined as any behavior characterized by an energy expenditure <1.5 METs while in a sitting or reclined position and is associated with a higher risk of hospitalization and death in the general population.[329]

Physical activity improves insulin sensitivity, lowers inflammatory markers, and improves endothelial function.[330–332] These, in turn, are associated with an improvement in CVD and all-cause mortality in the general population and those with kidney disease.[322] Higher levels of physical activity are favorably associated with measures of kidney function and damage.[322] In the Nurses Health Study, a higher physical activity level was associated with lower albuminuria in nondiabetic women.[333] Recent studies have also shown that higher levels of physical activity are associated with a slower decline in eGFR.[322] In the National Health and Nutrition Examination Survey (NHANES) cohort, physical inactivity was associated with increased mortality risk in CKD and non-CKD populations.[334] Further, a tradeoff of lower sedentary duration with higher light-activity duration was associated with a lower hazard of death in the CKD subgroup (hazard ratio [HR]: 0.59; 95% CI: 0.35–0.98). Cumulatively, evidence from observational studies suggests numerous health benefits of physical activity in those with kidney disease.[311] However, clinical trials examining the benefits of physical activity and exercise in those with CKD are limited.[326] The Action for Health in Diabetes (Look AHEAD) study, a large multicenter RCT, demonstrated that an intensive lifestyle modification that increased the physical activity to 175 min/wk did not confer cardiovascular benefits among overweight/obese adults with T2D.[335] However, in a secondary analysis of this trial, investigators examined the impact of intensive lifestyle modification on development of very high-risk CKD, defined as either (i) eGFR <30 ml/min per 1.73 m^2 regardless of ACR; (ii) eGFR <45 ml/min per 1.73 m^2 and ACR ≥30 mg/g; or (iii) eGFR <60 ml/min per 1.73 m^2 and ACR >300 mg/g. Intervention reduced the incidence of the very high-risk category of CKD by 31%, suggesting that there are long-term benefits of lifestyle changes in those with diabetes and at risk for CKD.[335]

Practice Point 3.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.

Older adults often have difficulty and restrictions in performing certain types of activities. These stem from the presence of other chronic comorbid conditions such as peripheral neuropathy, and osteoarthritis, which pose limitations for certain types of exercise. Therefore, physicians and healthcare providers should first assess the baseline activity level and the type of activities performed by the patients, along with their underlying comorbidities (other than CVD), prior to making any recommendations. Although dedicated trials among dialysis patients with diabetes are lacking, few clinical trials have examined home-based and intradialytic interventions in those on maintenance dialysis. Simple home-based exercise programs have been shown to be feasible and

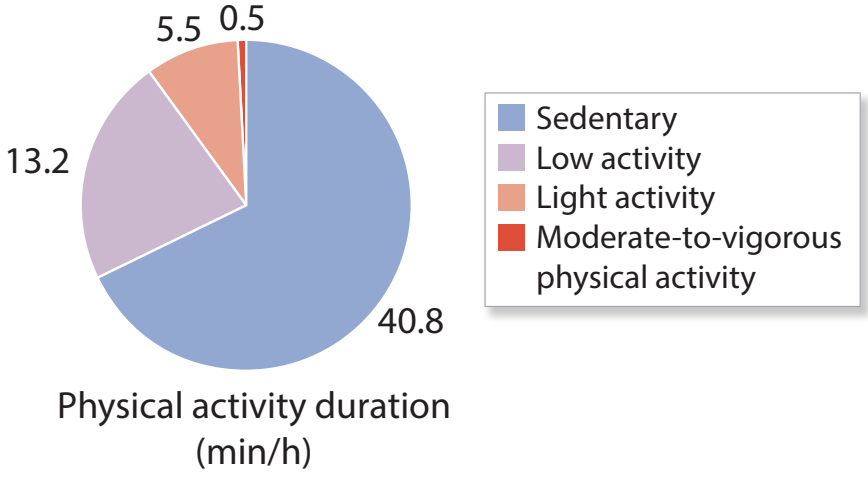


Figure 21 | Physical activity intensity levels in people with chronic kidney disease (CKD) in the US. Republished with permission of the American Society of Nephrology, *Clinical Journal of the American Society of Nephrology*, Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. Beddhu S, Wei G, Marcus RL, et al., volume 10, issue 7, 2015, permission conveyed through the Copyright Clearance Center, Inc.[313] Copyright © American Society of Nephrology.

offer health benefits in those on dialysis.[336] Similarly, intradialytic exercise programs have been shown to improve hemodialysis adequacy, exercise capacity, depression, and quality of life for those on hemodialysis, and can be offered where it is available.[337,338]

Practice Point 3.2.2: Patients should be advised to avoid sedentary behavior.

CKD patients are often sedentary, which is associated with an increased risk of mortality.[313] In addition, they have limited exercise tolerance and may not able to do longer periods of exercise. Thus, patients with CKD should be encouraged to do many short bouts of exercise (less intensity), as they still offer health benefits. Recent data indicate that the accumulated amount of activity over a week is critical (i.e., even shorter bouts of activities over the course of a week yield clinical benefits similar to those accomplished with intense physical activity).[1] Thus, when possible, activity should be spread throughout the week to maximize benefits.

Practice Point 3.2.3: For patients 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).

In those with CKD, sarcopenia is common and is related to adverse outcomes. Patients should engage in multicomponent physical activities, which include aerobic and muscle-strengthening activities along with balance-training activities as tolerated (Figure 22).[339] Benefits of muscle strengthening are often underappreciated. They promote weight maintenance and maintenance of lean body mass while a person is attempting to lose weight. These benefits can vary, and some patients may not perform certain types of exercises. Hence, recommendations for intensity and type of activity should be individualized based on their age, comorbid conditions, and activity status at baseline also. Depending on the availability of resources, referral to a physical activity specialist to provide guidance about the type and amount of exercise can be considered.

Practice Point 3.2.4: Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR ≥30 ml/min per 1.73 m^2.

Obesity (defined by body mass index [BMI] >30 kg/m^2) is an independent risk factor for kidney disease progression and CVD.[340] Among Asian populations, having a BMI >27.5 kg/m^2 increases the risk for adverse outcomes.[341] Pooled data from 40 countries (including approximately 5.5 million adults) suggest that higher BMI, waist circumference, and waist-to-height ratio are independent risk factors for kidney function decline and death in individuals who have normal or reduced levels of eGFR.[342] Current evidence suggests that intentional weight loss may reduce urinary albumin excretion, improve blood pressure, and offer potential kidney benefits in those with mild to moderate kidney disease.[343,344] Physicians should assess the patients' interest in losing weight and recommend increasing physical activity and appropriate dietary modifications in those who are obese, particularly when the eGFR is ≥30 ml/min per 1.73 m^2.

With an eGFR <30 ml/min per 1.73 m^2, and kidney failure treated with dialysis, patients may spontaneously reduce dietary intake, and malnutrition and muscle-wasting are potential concerns. Often, differentiating unintentional from intentional weight loss can be challenging in those with decline in kidney function. Further, higher BMI has been associated with better outcomes among patients treated with

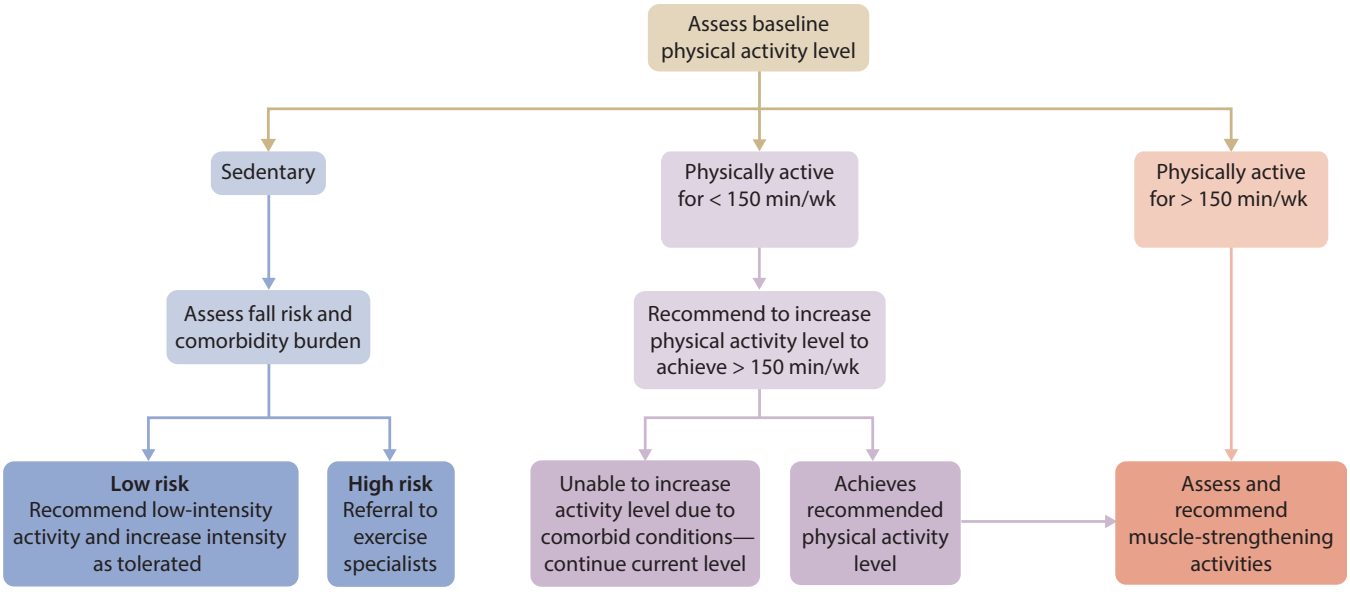


Figure 22 | Suggested approach to address physical inactivity and sedentary behavior in chronic kidney disease (CKD).

dialysis, and whether intentional weight loss offers health benefits is unclear in this population.[345] Therefore, depending on individual context, recommending intentional weight loss may not be appropriate for some patients with advanced CKD.

Research recommendations

- Further studies should be conducted to compare the benefits and risks of various intensities (light, moderate, and vigorous) and types of physical activity in those with diabetes and CKD.
- CKD patients are at higher risk of developing sarcopenia, which contributes to adverse outcomes. Resistance training could improve muscle mass; however, there is a lack of data for resistance training in CKD. Other clinical practice guidelines recommend that older adults should consider including resistance training as a component of their physical activity program. Prospective studies addressing the benefits and safety of resistance training in CKD are warranted.
- Studies testing physical activities such as yoga and other light-intensity physical activity as a replacement for sedentary behavior are needed.
- Potential ethnic differences in responses to physical activity should be explored in future studies so that personalized recommendations can be made.

Chapter 4: Glucose-lowering therapies in patients with T2D and CKD

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with both metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control (Figure 23).

Lifestyle therapy is the cornerstone of management for patients with T2D and CKD. In addition, metformin and SGLT2i should be used in combination as first-line treatment for most patients with suitable eGFR (Figures 23 and 25). SGLT2i are recommended as part of comprehensive care of patients with T2D and eGFR ≥20 ml/min per 1.73 m^2 because they have been proven to reduce risks of CKD progression and major CVD events, especially heart failure (see Section 1.3). These benefits of SGLT2i do not appear to be mediated by glycemia. Nonetheless, SGLT2i do also lower blood glucose, with improvements in HbA1c that are modest and diminished at low eGFR. Similarly, metformin is an effective, safe, and inexpensive medication for first-line treatment of T2D when eGFR is >30 ml/min per 1.73 m^2 (see Section 4.1). Therefore, a combination of metformin and SGLT2i is a logical foundation for glycemic control in suitable patients with T2D. Additional glucose-lowering drugs can be added to this base drug therapy as needed to achieve glycemic targets. GLP-1 RA are generally preferred because they are safe and effective glucose-lowering agents with eGFR as low as 15 ml/min per 1.73 m^2, reduce risk of ASCVD events even when eGFR is <60 ml/min per 1.73 m^2, lower albuminuria, and may slow eGFR decline. These recommendations are guided in large part by results of recent large RCTs, summarized in Figure 24 and detailed in Sections 1.3, 4.1, and 4.2.

Practice Point 4.2: Most patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i.

Both metformin (see Section 4.1) and SGLT2i agents (see Section 1.3) are preferred glucose-lowering medications for patients with T2D, CKD, and suitable eGFR. Metformin and SGLT2i each reduce the risk of developing diabetes complications with a low risk of hypoglycemia. Metformin has been proven to be a safe, effective, and inexpensive foundation for glycemic control in T2D, with modest long-term benefits for the prevention of diabetes complications. In comparison, SGLT2i have weaker effects on HbA1c, particularly with an eGFR <60 ml/min per 1.73 m^2, but they have large effects on reducing CKD progression and CVD events, especially heart failure, which appear to be independent of eGFR.[92,97]

In most patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2, metformin and an SGLT2i can be used safely and effectively together. Metformin should not be used for

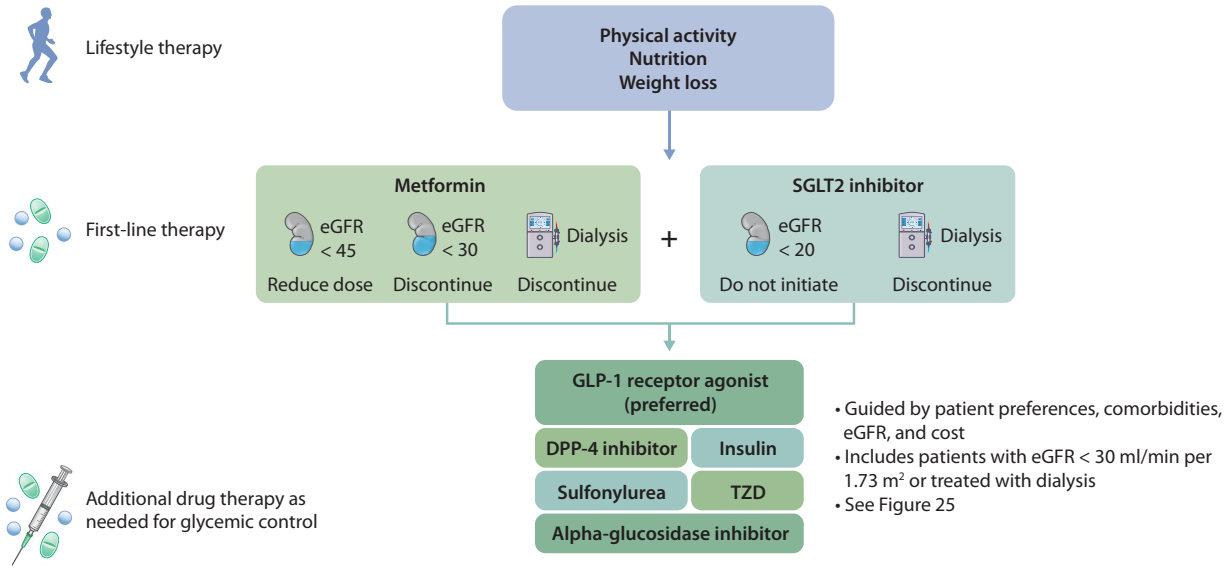


Figure 23 | Treatment algorithm for selecting glucose-lowering drugs for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

			Primary outcome		Kidney outcomes		
Drug	**Trial**	**Kidney-related eligibility criteria**	**Primary outcome**	**Effect on primary outcome**	**Effect on albuminuria or albuminuria-containing composite outcome**	**Effect on GFR loss***	**Adverse effects**
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
	EMPEROR-Preserved	No criteria	CV death or hospitalization for HF	↓	NA	↔	Genital and urinary tract infections, hypotension
	EMPEROR-Reduced	eGFR >20 ml/min per 1.73 m²	CV death or hospitalization for HF	↓	NA	↓↓	Genital tract infections
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [>30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m²	Progression of CKD†	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death‡	↔/↓	↓	↓↓	Genital mycotic infections, DKA
	DAPA-CKD	eGFR 25–75 ml/min per 1.73 m²	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from renal or CV causes	↓↓	↓↓	↓↓	Volume depletion
	DAPA-HF	eGFR ≥30 ml/min per 1.73 m²	CV death or worsening HF	↓	NA	↔	None notable
Ertugliflozin	VERTIS-CV	No criteria	MACE	↔	NA	↔	Genital mycotic infection, urinary tract infections
Sotagliflozin	SCORED	eGFR 25–60 ml/min per 1.73 m²	Deaths from CV causes, hospitalizations for HF, and urgent visits for HF	↓	NA	↔	DKA, GI, genital mycotic infections, volume depletion
	SOLOIST	No criteria	Deaths from CV causes and hospitalizations and urgent visits for HF	↓↓	NA	NA	Severe hypoglycemia
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↓	↔	None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔	GI
Semaglutide§	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↔	↔	None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↔	NA	Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔	GI
Efpeglenatide	AMPLITUDE-O	eGFR 25–59.9 ml/min per 1.73 m²	MACE	↓	↓↓	↔	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥15 ml/min per 1.73 m²	MACE	↔	↓	↔	HF; any hypoglycemic event (minor and major) also more common
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	↔	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥15 ml/min per 1.73 m²	Progression of CKD†	↔	↓	↔	None notable

Figure 24 | Overview of select large, placebo-controlled clinical outcome trials assessing the benefits and harms of sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. ACR, albumin-creatinine ratio; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GI, gastrointestinal symptoms (e.g., nausea and vomiting); HF, hospitalization for heart failure; MACE, major adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death (3-point MACE), with or without the addition of hospitalization for unstable angina (4-point MACE); NA, data not published;. ↔, no significant difference. ↓, significant reduction in risk, with hazard ratio (HR) estimate >0.7 and 95% confidence interval (CI) not overlapping 1. ↓↓, significant reduction in risk, with HR estimate ≤0.7 and 95% CI not overlapping 1. *Variable composite outcomes that include loss of eGFR, kidney failure, and related outcomes. †Progression of CKD defined in CREDENCE as doubling of serum creatinine, kidney failure, or death from kidney or cardiovascular causes and in CARMELINA as 40% decline in eGFR, kidney failure, or renal death. ‡DECLARE-TIMI 58 dual primary outcomes: (i) MACE and (ii) the composite of hospitalization for heart failure or CV death. §SUSTAIN-6: injectable semaglutide; PIONEER 6: oral semaglutide.

eGFR <30 ml/min per 1.73 m^2, whereas SGLT2i can be used for patients with eGFR as low as 20 ml/min per 1.73 m^2 for the cardiovascular and kidney benefits as part of comprehensive care of patients with CKD. The majority of the participants in the SGLT2i cardiovascular outcome trials were also treated with metformin, and many patients with T2D require more than 1 glucose-lowering medication to meet glycemic targets. The combination of metformin and an SGLT2i is logical because they have different mechanisms of action, and neither carries increased risk of hypoglycemia. Even when glycemic targets are achieved on metformin, an SGLT2i should be added in these patients for the beneficial effect on CKD progression and CVD risk (see Section 1.3).

For patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 not currently treated with glucose-lowering drugs (i.e., "drug naïve" patients), there are no high-quality data comparing initiation of glucose-lowering therapy with metformin first versus an SGLT2i first. Given the historical role of metformin as the initial drug treatment for T2D, and the fact that most patients in cardiovascular outcome trials treated with SGLT2i were first treated with metformin, it is logical to initiate metformin first for most patients, with the anticipation that SGLT2i should be added soon after. When sequencing multiple beneficial therapies, it is critical to ensure timely follow-up and institution of step-wise plans, avoiding treatment inertia (see Chapter 1). Initial combination therapy is also a reasonable option when education and monitoring for multiple potential adverse effects are feasible. Using low doses of both an SGLT2i and metformin may be a practical approach to managing glycemia, delivering the kidney and heart protection benefits of an SGLT2i (which do not appear to be dose dependent), and minimizing drug exposure. For patients who have little or no need for pharmacologic agents to control glycemia, or who cannot tolerate metformin, treatment with an SGLT2i alone is reasonable in order to reduce risks of CKD progression and CVD events.

Metformin should be initiated in patients with T2D and an eGFR ≥30 ml/min per 1.73 m^2 and should be discontinued when eGFR falls below 30 ml/min per 1.73 m^2 to reduce risk of lactic acidosis (Figure 23; Sections 1.3 and 4.1).[143] SGLT2i can be initiated for patients with an eGFR ≥20 ml/min per 1.73 m^2 (see Section 1.3). For patients whose eGFR subsequently declines below these initiation thresholds, the SGLT2i can be continued until initiation of kidney replacement therapy, in accordance with the approach studied in the CREDENCE and DAPA-CKD trials.[93,94]

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 25).

Some patients with T2D will not achieve glycemic targets with lifestyle therapy, metformin, and SGLT2i, or they will not be able to use these interventions due to intolerances, low eGFR, or other restrictions. Glucose-lowering agents other than metformin and SGLT2i will likely be needed in these situations. GLP-1 RA are generally preferred because of their demonstrated cardiovascular benefits, particularly among patients with established ASCVD even with eGFR <60 ml/min per 1.73 m^2,[346] and their benefits of reducing albuminuria and slowing eGFR decline (see Section 4.3).[346,347] Other classes of glucose-lowering agents may also be used, considering the patient factors detailed in Figure 25. DPP-4 inhibitors lower blood glucose with low risk of hypoglycemia but have not been shown to improve kidney or cardiovascular outcomes and should not be used in combination with GLP-1 RA.[348] All glucose-lowering medications should be selected and dosed according to eGFR.[349] For example, sulfonylureas that are long-acting or cleared by the kidney should be avoided at low eGFRs.[349]

4.1 Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin *(1B)*.

This recommendation places a high value on the efficacy of metformin in lowering HbA1c level, its widespread availability and low cost, its good safety profile, and its potential benefits in weight gain prevention and cardiovascular protection. The recommendation places a low value on the lack of evidence that metformin has any kidney protective effects or mortality benefits in the CKD population.

Key information

Balance of benefits and harms. Metformin is an effective antiglycemic agent and has been shown to be effective in reducing HbA1c in patients with T2D, with low risks for hypoglycemia in both the general population and patients with CKD. The United Kingdom Prospective Diabetes Study (UKPDS) showed that metformin monotherapy in obese individuals achieved similar reductions in HbA1c levels and fasting plasma glucose levels, with lower risk for hypoglycemia, when compared to those given sulfonylureas or insulin.[350] Moreover, a systematic review demonstrated that metformin monotherapy was comparable to thiazolidinediones (pooled mean difference in HbA1c: –0.04%; 95% CI: –0.11–0.03) and sulfonylurea (pooled mean difference in HbA1c: 0.07%; 95% CI: –0.12–0.26) in HbA1c reduction, but was more effective than DPP-4 inhibitors (pooled mean difference in HbA1c: –0.43%; 95% CI: –0.55 to –0.31).[351,352] This result had the added advantage of reduced risks of hypoglycemia when metformin was compared with sulfonylureas in patients with normal kidney function (odds ratio [OR]: 0.11; 95% CI: 0.06–0.20) and impaired kidney function (OR: 0.17; 95% CI: 0.11–0.26).[352]

In addition to its efficacy as an antiglycemic agent, studies have demonstrated that treatment with metformin is effective in preventing weight gain and may achieve weight reduction

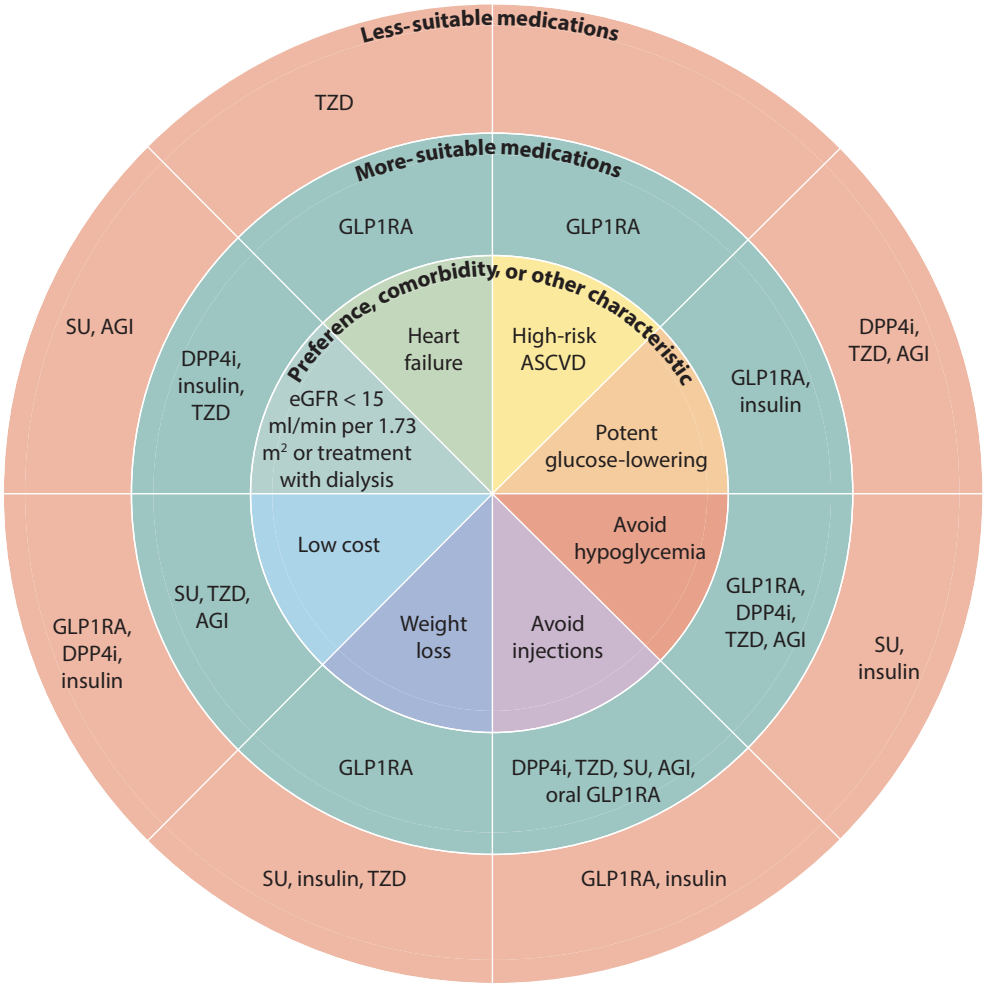


Figure 25 | Patient factors influencing the selection of glucose-lowering drugs other than sodium–glucose cotransporter-2 inhibitor (SGLT2i) and metformin in type 2 diabetes (T2D) and chronic kidney disease (CKD). AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; TZD, thiazolidinedione.

in obese patients. Results from the UKPDS study demonstrated that patients allocated to metformin did not show a change in mean body weight at the end of the 3-year study period, whereas body weight increased significantly with sulfonylurea and insulin treatment.[350] Similarly, this effect was reproduced in an analysis of a subgroup of patients in the UKPDS study who failed diet therapy and were subsequently randomized to metformin, sulfonylurea, or insulin therapy, with patients allocated to the metformin group having the least amount of weight gain.[245] Likewise, the same systematic review earlier showed that metformin treatment led to greater weight reduction compared to sulfonylurea (–2.7 kg; 95% CI: –3.5 to –1.9), thiazolidinediones (–2.6 kg; 95% CI: –4.1 to –1.2), or DPP-4 inhibitors (–1.3 kg; 95% CI: –1.6 to –1.0).[351,352]

In addition, treatment with metformin may be associated with protective effects against cardiovascular events, beyond its efficacy in controlling hyperglycemia in the general population. The UKPDS study suggested that among patients allocated to intensive blood glucose control treatment, metformin had a greater effect than sulfonylureas or insulin for reduction in diabetes-related endpoints, which included death from fatal or nonfatal myocardial infarction, angina, heart failure, and stroke.[245] An RCT performed in China, the Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease (SPREAD-DIMCAD) study, looked at the effect of metformin versus glipizide on cardiovascular events as a primary outcome. The study suggested that metformin has a potential benefit over glipizide on cardiovascular outcomes in high-risk patients, with a reduction in major cardiovascular events over a median follow-up of 5 years.[353] Indeed, in a systematic review, the signal for a reduction in cardiovascular mortality was again detected, with RR of 0.6–0.7 from RCTs in favor of metformin compared with sulfonylureas.[352]

Despite the potential benefits on cardiovascular mortality, the effects of metformin on all-cause mortality and other diabetic complications appeared to be less consistent in the

general population. The systematic review did not demonstrate any advantage of metformin over sulfonylureas in terms of all-cause mortality or microvascular complications.[352] There was even a suggestion in the UKPDS that early addition of metformin in sulfonylurea-treated patients was associated with an increased risk of diabetes-related death of 96% (95% CI: 2%–275%, $P = 0.039$).[245]

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of about 5 hours.[354] Phenformin, which was a related biguanide, was withdrawn from the market in 1977 because of its association with lactic acidosis. Consequently, the FDA applied a boxed warning to metformin, cautioning against its use in CKD in which the drug excretion may be impaired, thereby increasing the risk of lactic acid accumulation.[355] However, the association between metformin and lactic acidosis had been inconsistent, with literature reviews even refuting this concern,[356] including in patients with an eGFR of 30–60 ml/min per 1.73 m^2.[357] Consequently, the FDA revised its warning regarding metformin use in patients with CKD, switching from a creatinine-based restriction to include eligible patients with moderate CKD and an eGFR ≥30 ml/min per 1.73 m^2.[358]

Although the effect of heart protection with metformin use is studied mainly in the general population, evidence of this benefit in patients with CKD, especially those with reduced eGFR, is less consistent. A systematic review considered the association of all-cause mortality and MACE with treatment regimens that included metformin in patient populations for which metformin use is traditionally taken with precautions.[359] There were no RCTs, and only observational studies were included in the analysis of the CKD cohort. All-cause mortality was found to be 22% lower for patients on metformin treatment than for those not receiving it (HR: 0.78; 95% CI: 0.63–0.96), whereas there was no difference in MACE-related diagnoses with metformin use in 1 study. However, a second study that had examined MACE outcomes with metformin use suggested that metformin treatment was associated with a slightly lower readmission rate for congestive heart failure (HR: 0.91; 95% CI: 0.84–0.99). The signal for heart protection in the CKD cohort appears to be poor; the lackluster quality of the evidence and the observational nature of the studies in this population preclude any definitive conclusion on the cardiovascular benefits of metformin treatment in patients with reduced eGFR.

Quality of evidence. A search of the Cochrane Kidney and Transplant Registry identified no RCTs that had been conducted to evaluate the use of metformin in patients with T2D and CKD assessing cardiovascular and kidney protection as primary outcomes. The evidence that forms the basis of this clinical recommendation is extracted from RCTs and systematic reviews performed in the general population. The Work Group also considered the outcomes of studies that included patients with T2D and CKD, which were all observational in nature.

Values and preferences. The efficacy of HbA1c reduction, the good safety profile including a lower risk of hypoglycemia, and the low cost of metformin were judged to be critically important to patients. The Work Group assessed the benefit of weight reduction compared to use of insulin and sulfonylurea to be an important consideration, and patients who value weight reduction would prefer to be treated with metformin compared to having no treatment or other treatments. In addition, being widely available at low cost would make metformin a relevant initial treatment option in low-resource settings.

Resource use and costs. Metformin is among the least-expensive antiglycemic medications and is widely available. In resource-limited settings, this drug is affordable and may be the only drug available.

Considerations for implementation. Dose adjustments of metformin are required with a decline in the eGFR, and there are currently no safety data for metformin use in patients with an eGFR <30 ml/min per 1.73 m^2 or in those who are on dialysis. Patients will, therefore, need to be switched off metformin when the eGFR falls below 30 ml/min per 1.73 m^2. These practical issues are addressed in the practice points.

Different formulations of metformin. Typically, metformin monotherapy has been shown to lower HbA1c by approximately 1.5%.[360,361] Figure 26 outlines the different formulations, and their respective recommended doses, of metformin available.

Metformin is generally well-tolerated, although gastrointestinal adverse events may be experienced in up to 25% of patients treated with the immediate-release form of metformin, with treatment discontinuation occurring in about 5%–10% of patients.[362–364] Clinical studies have demonstrated that the tolerability of extended-release metformin was generally comparable to or even increased compared to the immediate-release formulation. In a 24-week double-

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin, Immediate Release	Tablet, Oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum: 2.55 g/day
Metformin, Extended Release	Tablet, Oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/day

Figure 26 | Different formulations of metformin.

blind RCT of adults with T2D who were randomly assigned to 1 of 3 extended-release metformin treatment regimens (1500 mg once daily, 1500 mg twice daily, or 2000 mg once daily) or immediate-release metformin (1500 mg twice daily), the overall incidence of adverse events was noted to be similar for all treatment groups, although fewer patients in the extended-release group developed nausea during the initial dosing period (2.9%, 3.9%, and 2.4% for the respective extended-release treatment regimens vs. 8.2% in the immediate-release group, $P = 0.05$).[365] Moreover, fewer patients who received the extended-release metformin discontinued treatment because of gastrointestinal side effects during the first week (0.6% vs. 4.0%). Another RCT of 532 treatment-naïve Chinese patients with T2D (the Comparison of metfOrmin XR to IR as moNotherapy in the Newly diagnoSed Type 2 diabEtes Patients for the gastroiNtestinal Tolerability and Efficacy [CONSENT] study), however, showed comparable gastrointestinal adverse events between patients receiving monotherapy with immediate-release versus extended-release metformin (23.8% vs. 22.3%, respectively).[366]

In view of the overall benefits of metformin treatment, and the possibility of improved tolerability of extended-release metformin, patients who experienced significant gastrointestinal side effects from the immediate-release formulation could be considered for a switch to extended-release metformin and monitored for improvement of symptoms.

Rationale

This recommendation places a higher value on the many potential advantages of metformin use in the general population, which include its efficacy in lowering HbA1c, its benefits in weight reduction and cardiovascular protection, its good safety profile, the general familiarity with the drug, its widespread availability and low cost; and a lower value on the lack of evidence that metformin has any kidney protective effects or mortality benefits.

This is a strong recommendation, as the Work Group judged that metformin would likely be the initial drug of choice for all or nearly all well-informed patients, due to its widespread availability and low cost, especially in low-resource settings. The Work Group also judged that the majority of physicians, if not all, will be comfortable in initiating metformin treatment due to familiarity with this drug, and its good safety profile.

Practice Point 4.1.1: Treat kidney transplant recipients with T2D and an eGFR ≥30 ml/min per 1.73 m^2 with metformin according to recommendations for patients with T2D and CKD.

The data for the use of metformin after kidney transplantation are less robust. Most of the evidence was derived from registry and pharmacy claims data, which showed that the use of metformin was not associated with worse patient or allograft survival.[367] One such analysis even suggested that metformin treatment after kidney transplantation was associated with significantly lower all-cause, malignancy-related, and infection-related mortality.[368] The Transdiab study was a pilot, randomized, placebo-controlled trial that recruited 19 patients with impaired glucose tolerance after kidney transplantation from a single center, and examined the efficacy and tolerability of metformin treatment.[369] Although there were no adverse signals from the trial, the number of patients recruited was unfortunately too small for any conclusive recommendations. In view of the lack of data against the use of metformin after transplantation, it is the judgment of the Work Group that the recommendation for metformin use in the transplant population be based on the eGFR, using the same approach as for the CKD group.

Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when the eGFR is <60 ml/min per 1.73 m^2 (Figure 27).

Given that metformin is excreted by the kidneys and there is concern for lactic acid accumulation with a decline in kidney function, it is important to monitor the eGFR at least annually when a patient is on metformin treatment. The frequency of monitoring should be increased to every 3–6 months as the eGFR drops below 60 ml/min per 1.73 m^2, with a view to decreasing the dose accordingly.

Practice Point 4.1.3: Adjust the dose of metformin when the eGFR is <45 ml/min per 1.73 m^2, and for some patients when the eGFR is 45–59 ml/min per 1.73 m^2 (Figure 27).

Figure 27 provides a suggested approach in adjusting the dose for metformin in accordance to the decline in kidney function:

- For an eGFR of 45–59 ml/min per 1.73 m^2, dose reduction may be considered in the presence of conditions that predispose patients to hypoperfusion and hypoxemia.
- The maximum dose should be halved when the eGFR declines to 30–45 ml/min per 1.73 m^2.
- Treatment should be discontinued when the eGFR declines to <30 ml/min per 1.73 m^2, or when the patient is initiated on dialysis, whichever is earlier.

Practice Point 4.1.4: Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years.

Metformin interferes with intestinal vitamin B12 absorption, and the NHANES found that biochemical vitamin B12 deficiency was noted in 5.8% of patients with diabetes on metformin, compared to 2.4% ($P = 0.0026$) of those not on metformin, and 3.3% ($P = 0.0002$) of patients without diabetes.[370] One study randomized patients with T2D on insulin to receive metformin or placebo and examined the development of vitamin B12 deficiency over a mean follow-up period of 4.3 years.[371] Metformin treatment was associated with a mean reduction of vitamin B12 concentration compared to placebo after approximately 4 years. However, clinical consequences of vitamin B12 deficiency with metformin

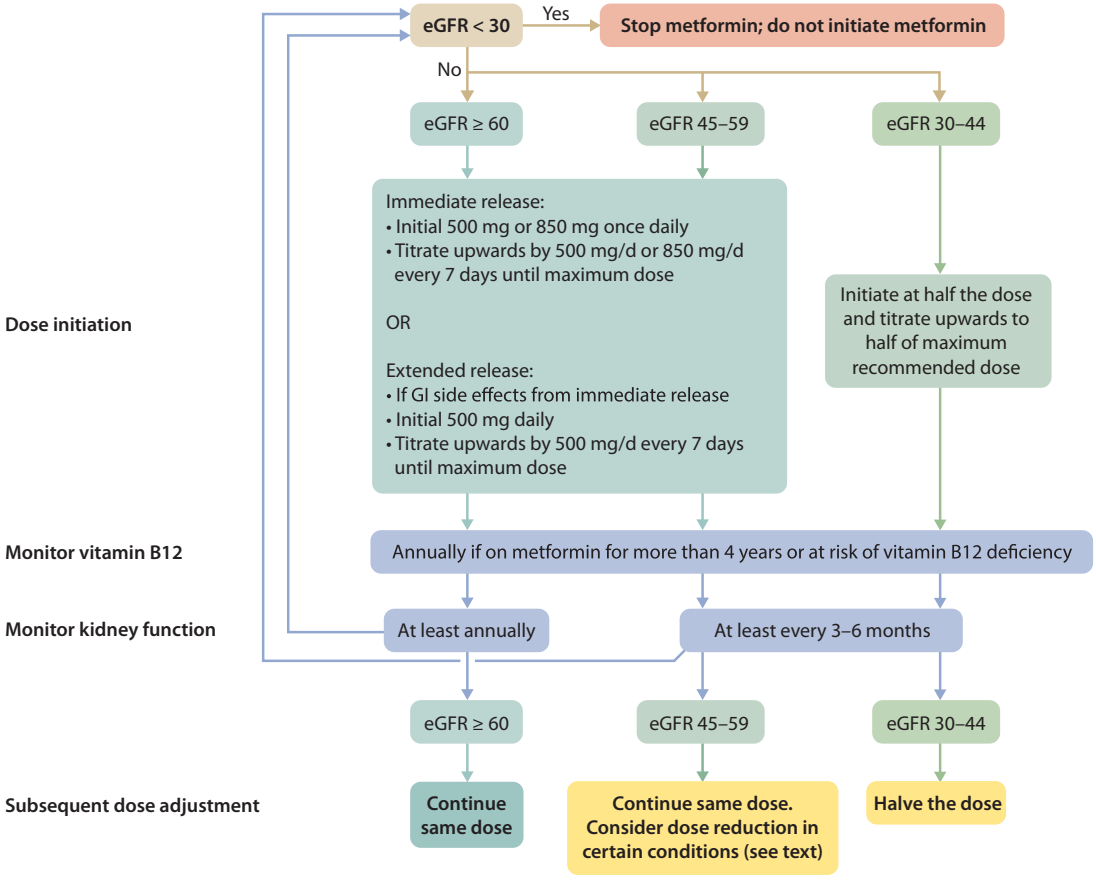


Figure 27 | Suggested approach in dosing metformin based on the level of kidney function. eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); GI, gastrointestinal.

treatment are uncommon, and it is the judgment of the Work Group that routine concurrent supplementation with vitamin B12 is unnecessary. In addition, the study demonstrated that the reduction in vitamin B12 concentration is increased with increasing duration of metformin therapy. Monitoring of vitamin B12 levels should be considered in patients who have been on long-term metformin treatment (e.g., >4 years) or in those who are at risk of low vitamin B12 levels (e.g., patients with malabsorption syndrome, or reduced dietary intake [vegans]).

Research recommendations

RCTs are needed to:

- Evaluate the safety, efficacy, and potential cardiovascular and kidney protective benefits of metformin use in patients with T2D and CKD, including those with an eGFR <30 ml/min per 1.73 m^2 or on dialysis.
- Evaluate the safety and efficacy of metformin in kidney transplant recipients.

4.2 Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

GLP-1 is an incretin hormone secreted from the intestine after ingestion of glucose or other nutrients. In the pancreas, it stimulates glucose-dependent release of insulin from beta cells and suppresses glucagon release from alpha cells. GLP-1 also slows gastric emptying and decreases appetite stimulation in the brain, facilitating weight loss. These incretin effects are reduced or absent in patients with diabetes.

Long-acting GLP-1 RA medications, which stimulate this pathway, have been shown to substantially improve glycemic control and confer weight loss. More importantly, though, several GLP-1 RA agents have been shown to reduce MACE in patients with T2D with HbA1c >7.0%, who were at high cardiovascular risk.[372–375] Additionally, these same GLP-1 RA agents have been shown to have kidney benefits by reducing albuminuria and slowing the rate of eGFR decline.[372,374,375]

Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

This recommendation places a high value on the cardiovascular and kidney benefits of long-acting GLP-1 RA treatment in patients with T2D and CKD, and a lower value on the costs and adverse effects associated with this class of drug.

Key information

Balance of benefits and harms. Data for cardiovascular and kidney outcomes, and cardiometabolic benefits, are summarized below.

Cardiovascular outcomes. There are currently 8 published large RCTs examining cardiovascular outcomes for injectable GLP-1 RA[347,372–382] and 1 trial of an oral GLP-1 RA (Figure 28).[383] Of these, 5 studies (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER],[379] Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6],[374] Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus [HARMONY],[373] and Researching Cardiovascular Events With a Weekly Incretin in Diabetes [REWIND],[372] and Effect of Efpeglenatide on Cardiovascular Outcomes [AMPLITUDE-O][347]) have confirmed cardiovascular benefit of 5 injectable GLP-1 RA with significant reductions in MACE for liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide respectively. The other agents (lixisenatide, exenatide, and oral semaglutide) have been shown to have cardiovascular safety, but without significant effects on cardiovascular risk reduction.

The LEADER trial (evaluating liraglutide) included 9340 individuals with T2D and HbA1c ≥7% with high cardiovascular risk defined as established CVD, CKD G3 or higher, age ≥60 years, or a major CVD risk factor.[379] Of note, the LEADER trial also included 220 individuals with an eGFR of 15–30 ml/min per 1.73 m^2. The LEADER trial compared once-daily liraglutide to placebo and followed participants for a median of 3.8 years for primary MACE outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. There was a 13% reduction in MACE (HR: 0.87; 95% CI: 0.78–0.97) conferred by liraglutide.

In the LEADER trial, the risk reduction for the primary composite MACE outcome was even greater among individuals with CKD G3a or greater severity (eGFR <60 ml/min per 1.73 m^2) compared to those with an eGFR ≥60 ml/min per 1.73 m^2 (HR: 0.69; 95% CI: 0.57–0.85 vs. HR: 0.94; 95% CI: 0.83–1.07, respectively, *P*-interaction = 0.01).[384] This benefit was seen across each separate cardiovascular outcome. Notably, liraglutide (compared to placebo) conferred an impressive 49% reduction for nonfatal stroke, with HR: 0.51 (95% CI: 0.33–0.80) for eGFR <60 ml/min per 1.73 m^2 versus HR: 1.07 (95% CI: 0.84–1.37) for eGFR ≥60 ml/min per 1.73 m^2. Although subgroup analyses should be considered cautiously, these findings suggest that efficacy among individuals with CKD is at least as great as that for those without CKD.

The SUSTAIN-6 trial (evaluating injectable semaglutide) enrolled 3297 patients with T2D and HbA1c ≥7% with CVD, CKD G3 or higher, or age ≥60 years with at least 1 major CVD risk factor.[374] A total of 83% of participants had CVD, CKD, or both, with 10.7% having CKD only and 13.4% having both CKD and CVD. SUSTAIN-6 found that once-weekly semaglutide compared to placebo reduced the primary composite MACE outcome by 26% (HR: 0.74; 95% CI: 0.58–0.95). In subgroup analysis, there was no evidence of effect heterogeneity by CKD subgroup, with similar MACE reduction for those with an eGFR <30 ml/min per 1.73 m^2 versus ≥30 ml/min per 1.73 m^2 (*P*-interaction = 0.98) and similar reduction for those with an eGFR <60 ml/min per 1.73 m^2 versus ≥60 ml/min per 1.73 m^2 (*P*-interaction = 0.37).

The HARMONY trial (evaluating albiglutide) evaluated 9463 participants with T2D and high cardiovascular risk with HbA1c ≥7%.[373] Of note, an eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion. HARMONY found that albiglutide (dosed once weekly) compared to placebo reduced the primary MACE outcome (cardiovascular death, myocardial infarction, or stroke) over a median duration of follow-up of 1.6 years in the overall cohort by 22% (HR: 0.78; 95% CI: 0.68–0.90). There was no significant heterogeneity of treatment benefit for the primary cardiovascular outcome among the eGFR subgroups of <60 ml/min per 1.73 m^2, ≥60–90 ml/min per 1.73 m^2, and ≥90 ml/min per 1.73 m^2 (*P*-interaction = 0.19). At this time, albiglutide is currently not available on the market, so this is not an option for patients.

The REWIND trial (evaluating dulaglutide) included 9901 adults with T2D with HbA1c of ≤9.5% (with no lower limit and mean HbA1c of 7.2%).[372,377] An eGFR <15 ml/min per 1.73 m^2 was an exclusion criterion. The REWIND trial enrolled a low proportion of patients with established CVD (31.5%); thus, it is largely considered a primary prevention trial. The REWIND trial also included a significant number of individuals with CKD. Over a median follow-up of 5.4 years, the primary MACE outcome (composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or CVD death) was 12% lower with once-weekly dulaglutide compared to placebo (HR: 0.88; 95% CI: 0.79–0.99). The reduction in primary cardiovascular outcome was similar among those with versus without previous CVD (*P*-interaction = 0.97).

The AMPLITUDE-O trial studied the cardiovascular safety of efpeglenatide in 4076 patients with T2D and high cardiovascular risk or CKD, including 89.6% with established CVD. Efpeglenatide was superior to placebo for the primary MACE outcome, with HR for the primary outcome of 0.73 (95% CI: 0.58–0.92), and comparable MACE risk reduction in participants with eGFR <71 ml/min per 1.73 m^2 with HR for primary outcome of 0.67 (95% CI: 0.50–0.91).[347]

In contrast, the Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA; lixisenatide)[381] and the EXenatide Study of Cardiovascular Event Lowering (EXSCEL; exenatide)[376,378] trials did not show a cardiovascular benefit with GLP-1 RA, nor did they find increased harm, confirming cardiovascular safety. Differences in the results of the ELIXA and EXSCEL trials, compared with the more favorable results seen in the LEADER, SUSTAIN, HARMONY, and REWIND trials, may stem from differences in GLP-1 RA molecular structures, half-lives, and formulations, study design, or the

	ELIXA	LEADER	SUSTAIN	EXSCEL	HARMONY	REWIND	PIONEER 6	AMPLITUDE-O	AWARD-7
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)	Efpeglenatide	Dulaglutide
Total number of participants	6068	9340	3297	14,752	9463	9901	3183	4076	577
% with CVD	100	81.3	83	73	100	31.5	84.7	89.6	Not reported
eGFR criteria for enrollment (ml/min per 1.73 m^2)	≥30	Most had eGFR ≥30, but did include 220 patients with eGFR 15 to 30	Not reported	≥30	≥30	≥15	≥30 (however 0.9% had eGFR <30)	25–59.9	Not reported
Mean eGFR at enrollment (ml/min per 1.73 m^2)	76	80	~75	76	79	76.9	74	72.4	38
% with eGFR <60 ml/min per 1.73 m^2	23	20.7 with eGFR 30 to 59 ml/min per 1.73 m^2, 2.4 with eGFR <30 ml/min per 1.73 m^2	28.5	22.9	Not reported	22.2	26.9	31.6	100 with CKD G3a–G4
ACR	19% with moderately increased albuminuria and 7% with severely increased albuminuria	Not reported	Not reported	3.5% with severely increased albuminuria	Not reported	7.9% with severely increased albuminuria	Not reported	Median 28.3 mg/g [2.83 mg/mmol]	44% with severely increased albuminuria
Follow-up time (yr)	2.08	3.8	2.1	3.2	1.6	5.4	1.36	1.81	1
CV outcome definition	CV death, MI, stroke, or hospitalization for unstable angina	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	MACE	NA
CV outcome results	HR: 1.02; 95% CI: 0.89–1.17	HR: 0.87; 95% CI: 0.78–0.97	HR: 0.74; 95% CI: 0.58–0.95	HR: 0.91; 95% CI: 0.83–1.00	HR: 0.78; 95% CI: 0.68–0.90	HR: 0.88; 95% CI: 0.79–0.99	HR: 0.79; 95% CI: 0.57–1.11	HR: 0.73; 95% CI: 0.58–0.92	NA
Kidney outcome (secondary end points)	New-onset severely increased albuminuria and doubling of SCr	New-onset persistent severely increased albuminuria, persistent doubling of the SCr level, kidney failure, or death due to kidney disease	Persistent severely increased albuminuria, persistent doubling of SCr, a CrCl of <45 ml/min, or need for KRT	Two kidney composite outcomes: 1) 40% eGFR decline, kidney replacement, or renal death, 2) 40% eGFR decline, kidney replacement, renal death, or severely increased albuminuria	Not reported	New severely increased albuminuria ACR of >33.9 mg/mmol [>339 mg/g], a sustained fall in eGFR of 30% from baseline, or use of KRT	Not reported	Composite of incident severely increased albuminuria (ACR >300 mg/g or >33.9 mg/mmol), increase in ACR ≥30%, sustained decrease in eGFR by ≥40% for ≥30 days, or kidney replacement therapy for ≥90 days, or a sustained eGFR of <15 ml/min per 1.73 m^2 for ≥30 days	eGFR, ACR
Kidney outcome results	New-onset macroalbuminuria: adjusted HR: 0.81; 95% CI: 0.66–0.99, *P*=0.04; Doubling of SCr: adjusted HR: 1.16; 95% CI: 0.74–1.83, *P*=0.51	HR: 0.78; 95% CI: 0.67–0.92	HR: 0.64; 95% CI: 0.46–0.88	40% eGFR decline, kidney replacement, or renal death: adjusted HR: 0.87; 95% CI: 0.73–1.04, *P*=0.13; 40% eGFR decline, kidney replacement, renal death, or severely increased albuminuria: adjusted HR: 0.85; 95% CI: 0.74–0.98, *P*=0.03	Not reported	HR: 0.85; 95% CI: 0.77–0.93 Similar for eGFR ≥60 vs. <60 ml/min per 1.73 m^2, no albuminuria vs. albuminuria, no ACEi/ARB vs. ACEi/ARB	Not reported	Kidney composite outcome: HR: 0.68; 95% CI: 0.57–0.79	eGFR did not significantly decline (–0.7 ml/min per 1.73 m^2) with dulaglutide 1.5 mg or dulaglutide 0.75 mg, whereas eGFR decreased by –3.3 ml/min per 1.73 m^2 with insulin glargine

Figure 28 | Cardiovascular and kidney outcome trials for glucagon-like peptide-1 receptor agonists (GLP-1 RA). ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin–creatinine ratio; ARB, angiotensin II receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (ml/min per 1.73 m^2); G, glomerular filtration rate category; G3a–G4, estimated glomerular filtration rate 15–59 ml/min per 1.73 m^2; HR, hazard ratio; KRT, kidney replacement therapy; MI, myocardial infarction; NA, not available; SCr, serum creatinine.

patient populations studied. For example, the ELIXA trial had a high discontinuation and dropout rate.

The Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 study investigated the cardiovascular safety of an oral GLP-1 RA (oral semaglutide).[383] The study evaluated 3183 patients with T2D and high cardiovascular risk, CKD, or age >50 years with a major CVD risk factor. An eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion. Oral semaglutide was found to not be inferior to placebo for primary MACE outcomes. Furthermore, there was no difference in the primary outcome for participants with an eGFR <60 ml/min per 1.73 m^2 versus ≥60 ml/min per 1.73 m^2 (*P*-interaction = 0.80), with HR for primary outcome of 0.74 (95% CI: 0.41–1.33) for those with an eGFR <60 ml/min per 1.73 m^2.

A 2021 meta-analysis of the 8 trials of GLP-1 RA (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, PIONEER 6, and AMPLITUDE-O), which together included a total of 60,080 participants, evaluated pooled cardiovascular and kidney outcome data in participants with T2D, including those with CKD.[346] Compared to placebo, GLP-1 RA treatment conferred a reduction in cardiovascular death (HR: 0.87; 95% CI: 0.80–0.94), stroke (HR: 0.83; 95% CI: 0.76–0.92), myocardial infarction (HR: 0.90; 95% CI: 0.83–0.98), all-cause mortality (HR: 0.88; 95% CI: 0.82–0.94), and hospitalization for heart failure (HR: 0.90; 95% CI: 0.83–0.98). Of note, this is the first time a benefit for heart failure hospitalization has been demonstrated for the GLP-1 RA class of medications.

Kidney outcomes. The LEADER trial also examined the effects of liraglutide compared to placebo on a prespecified secondary composite kidney outcome (new-onset severely increased albuminuria, doubling of serum creatinine, kidney failure, or death from kidney disease).[379] Liraglutide conferred a significant 22% reduction in this composite kidney outcome (HR: 0.78; 95% CI: 0.67–0.92), driven primarily by reduction in new-onset severely increased albuminuria (HR: 0.74; 95% CI: 0.60–0.91). There was no difference between liraglutide and placebo in serum creatinine or kidney failure, and few deaths attributed to kidney disease occurred in the study.

In the SUSTAIN-6 trial, there was also a reduction in new or worsening nephropathy with semaglutide compared to placebo (HR: 0.64; 95% CI: 0.46–0.88).[374] This composite kidney outcome was defined as persistent severely increased albuminuria, persistent doubling of serum creatinine, a creatinine clearance of <45 ml/min, or need for kidney replacement therapy.

The REWIND trial also examined dulaglutide's benefit on CKD as a component of the secondary microvascular outcome.[372,377] There was a 15% reduction in the composite kidney outcome defined as new severely increased albuminuria (ACR of >33.9 mg/mmol [>339 mg/g]), sustained eGFR decline of 30% from baseline, or use of kidney replacement therapy with dulaglutide compared to placebo (HR: 0.85; 95% CI: 0.77–0.93). Similar to other GLP-1 RA trials, the strongest evidence for benefit was for new severely increased albuminuria (HR: 0.77; 95% CI: 0.68–0.87). Notably, in *post hoc* exploratory analyses, eGFR decline thresholds of 40% and 50% were significantly reduced by 30% and 46%, respectively. Of course, exploratory results must be interpreted cautiously and regarded as hypothesis-generating. There were no serious adverse events for kidney disease in the REWIND trial. Among the 9901 participants, 22.2% had an eGFR <60 ml/min per 1.73 m^2 at baseline, and 7.9% had severely increased albuminuria. The benefit on the composite kidney outcome was similar among those with an eGFR ≥60 ml/min per 1.73 m^2 or <60 ml/min per 1.73 m^2 (*P*-interaction = 0.65), and among subgroups defined by baseline albuminuria status and use of an ACEi or ARB. Of note, the HbA1c-lowering and blood pressure–lowering effects explained 26% and 15%, respectively, of the kidney benefits conferred by dulaglutide. Hence, not all of the benefit of GLP-1 RA can be explained by improvement in the conventional CKD risk factors.

Another important study that supports a potential kidney benefit and emphasizes the safety of a GLP-1 RA for glycemic control in the CKD population was the Assessment of Weekly Administration of LY2189265 (Dulaglutide) in Diabetes 7 (AWARD-7) trial, which compared dulaglutide to insulin glargine among patients with moderate-to-severe CKD.[382] Although glycemic indices were the primary outcome of the trial, kidney outcomes (eGFR and ACR) were the main secondary outcomes. AWARD-7 enrolled patients with T2D and CKD G3a–G4 (mean eGFR 38 ml/min per 1.73 m^2) who were being treated with an ACEi or ARB and found that dulaglutide conferred significantly less eGFR decline over 52 weeks (mean: –3.3 ml/min per 1.73 m^2 vs. –0.7 ml/min per 1.73 m^2) with either a lower dose (0.75 mg weekly) or higher dose (1.5 mg weekly) of dulaglutide, respectively, compared to insulin glargine. The benefits on eGFR were most evident in the severely increased albuminuria subgroup (mean: –5.5 ml/min per 1.73 m^2 vs. –0.7 ml/min per 1.73 m^2 and –0.5 ml/min per 1.73 m^2 over 52 weeks) with the lower and higher doses of dulaglutide, respectively. These benefits were accomplished with similar improvement in HbA1c (mean 1%) and comparable blood pressure levels between the dulaglutide and insulin glargine groups. Notably, rates of symptomatic hypoglycemia were reduced by half with dulaglutide compared to insulin glargine. Although there were the expected higher rates of gastrointestinal side effects, the overall safety profile of dulaglutide was confirmed in CKD G3a–G4. As a result, dulaglutide has received FDA approval for glycemic control in T2D with eGFR as low as 15 ml/min per 1.73 m^2. In a prespecified exploratory analysis of AWARD-7, risk for 40% eGFR decline or kidney failure treated by dialysis or kidney transplant was reduced by more than half, and in those with macroalbuminuria, the relative risk for this outcome was reduced by 75% (HR: 0.25; 95 % CI: 0.10–0.68).[385]

In the 2021 meta-analysis, 8 cardiovascular outcomes trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, PIONEER 6, and AMPLITUDE-O), GLP-1 RA treatment reduces risk for a broad composite kidney outcome (development of new severely increased albuminuria, decline

in eGFR, or rise in serum creatinine, progression to kidney failure, or death from kidney disease cause; HR: 0.79; 95% CI: 0.73–0.87) compared to placebo in populations with T2D.[346] In these groups selected for high CVD risk, kidney endpoints were driven largely by reduction in albuminuria, as to be expected. Excluding severely increased albuminuria, the association of GLP-1 RA with worsening kidney function did not achieve statistical significance, but the signal points toward benefit (HR: 0.86; 95% CI: 0.72–1.02).

A major limitation is that results have not been reported from a clinical trial enrolling a study population selected for CKD or in which kidney outcomes were the primary outcomes. However, a clinical trial of GLP-1 RA with a primary kidney disease outcome is forthcoming with the ongoing Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial (NCT03819153) that is evaluating whether injectable semaglutide 1 mg weekly among patients with T2D and an eGFR of 25–50 ml/min per 1.73 m^2 or with severely increased albuminuria on a background ACEi or ARB therapy confers kidney benefit. A companion mechanistic trial, the Renal Mode of Action of Semaglutide in Patients With Type 2 Diabetes and Chronic Kidney Disease study (REMODEL, NCT04865770) is examining effects of semaglutide on kidney inflammation, perfusion, and oxygenation by magnetic resonance imaging and kidney biopsies.[386]

Cardiometabolic benefits. The favorable effects of GLP-1 RA on risk factors (i.e., reductions in glycemia, blood pressure, and body weight) may contribute to the favorable cardiovascular and CKD outcomes versus placebo or insulin therapy. GLP-1 RA are more potent glucose-lowering agents compared to SGLT2i in the CKD population and confer greater weight-loss potential.

Harms. Most GLP-1 RA are administered subcutaneously. Some patients may not wish to take an injectable medication. There is currently 1 FDA-approved oral GLP-1 RA (semaglutide).

Side effects of GLP-1 RA may preclude use of a GLP-1 RA in some patients. There is risk of adverse gastrointestinal symptoms (nausea, vomiting, and diarrhea). The gastrointestinal side effects are dose-dependent and may vary across GLP-1 RA formulations.[387] There also might be injection-site reactions and an increase in heart rate with this therapy, and GLP-1 RA should be avoided in patients at risk for thyroid C-cell (medullary thyroid) tumors and with a history of acute pancreatitis.

Exenatide and lixisenatide are not recommended at low eGFR, and given that the ELIXA[381] and EXSCEL[376,378] trials did not prove any cardiovascular benefit with these agents, the priority is to use one of the other available GLP-1 RA, which have shown CVD and CKD benefits (i.e., liraglutide, semaglutide, and dulaglutide). Notably, effects of GLP-1 RA on cardiovascular and CKD outcomes appear not to be entirely mediated through improved risk factors. Treatment with GLP-1 RA may be used for kidney and heart protection as well as to manage hyperglycemia. Initiation of a GLP-1 RA must take into account other glucose-lowering agents, especially those associated with hypoglycemia, which may require changes to these medications. Of note, in the largest meta-analyses conducted to date with 8 GLP-1 RA trials including 60,080 participants, there were no increased risks of hypoglycemia, pancreatitis, or pancreatic cancer.[346]

Although GLP-1 RA and SGLT2i reduce MACE to a similar degree, GLP-1 RA may be preferred for ASCVD, whereas there is currently stronger evidence for SGLT2i for reduction in heart failure and CKD progression. For patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2, SGLT2i agents are preferred over GLP-1 RA as initial kidney and heart protective agents. However, in light of the aforementioned beneficial effects of GLP-1 RA on cardiovascular and kidney outcomes in patients with T2D, GLP-1 RA are an excellent addition for patients who have not achieved their glycemic target or as an alternative for patients unable to tolerate metformin and/or an SGLT2i. GLP-1 RA may also be useful for reducing albuminuria.

GLP-1 RA are contraindicated for patients with a history of medullary thyroid cancer or with multiple endocrine neoplasia 2 (MEN-2), although these are rare conditions, and for patients with a history of acute pancreatitis.

In summary, the overall safety data for liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide from the LEADER, SUSTAIN 6, HARMONY, REWIND, AWARD-7, and AMPLITUDE-O clinical trials are acceptable, and the cardiovascular benefits are considerable, with additional benefits conferred for kidney outcomes.

Quality of evidence. The overall quality of the evidence was rated as moderate. This recommendation comes from well-conducted, double-blinded, placebo-controlled RCTs of GLP-1 RA that enrolled patients with CKD,[347,372–376,378,379,381–384,388] a meta-analysis of these 8 RCTs combining efficacy data for cardiovascular and kidney outcomes,[346] and an update to the 2018 Cochrane systematic review and meta-analysis[93,129] in patients with diabetes and CKD conducted by the ERT (Supplementary Table S23[347,372–376,378,380–383,388–396]) From these data, there is moderate quality of evidence that GLP-1 RA reduce MACE among patients with T2D. The quality of the evidence was downgraded to moderate because of the inconsistency of the data, with an I^2 of 55%, with some studies demonstrating benefit and others little to no difference of GLP-1 RA compared to placebo/standard of care.

There also appears to be favorable benefits in broad composite kidney outcomes, largely driven by reduction in severely increased albuminuria, with less evidence to support benefit for harder kidney outcomes (Supplementary Table S23[347,372–376,378,380–383,388–396]) There also has not been a designated trial published to date with a primary endpoint of kidney outcomes, although the ongoing FLOW trial (NCT03819153) will determine whether GLP-1 RA can slow progression of CKD in T2D.

- *Study design:* There have now been multiple RCTs, with an adequate number of study participants, that have evaluated the benefit of GLP-1 RA on clinically meaningful cardiovascular outcomes. CKD outcomes have been examined as either predefined secondary outcomes or exploratory outcomes. As discussed above, a systematic review and meta-analysis of RCTs confirmed evidence of benefit for important major cardiovascular outcomes, as well as broad kidney composite outcome, largely driven by reduction in urinary albumin excretion.[346]
- *Risk of bias:* The risk of bias is low, as the 8 large RCTs studies demonstrated good allocation concealment and adequate blinding, with complete accounting for all patients and outcome events. In the aforementioned meta-analysis of 8 RCTs of GLP-1 RA, the authors found that all trials were of high quality and met criteria for low risk of bias as assessed by the Cochrane Risk of Bias tool.[346] However, in the updated Cochrane review that focused on people with diabetes and CKD found unclear reporting of allocation concealment and blinding in other included trials which downgraded the evidence for hypoglycemia requiring third-party assistance, hyperkalemia, HbA1c, eGFR loss, change in body weight, and body mass index.
- *Consistency:* The consistency is moderate to high across the trials. In the analysis of patients with CKD, heterogeneity was observed for the primary cardiovascular outcome (3-point MACE; $I^2 = 55\%$). No heterogeneity was observed for secondary kidney outcomes across baseline eGFR and baseline ACR groups. Other important outcomes such as HbA1c ($I^2 = 86\%$) and eGFR loss ($I^2 = 70\%$) also demonstrated high heterogeneity.
- *Indirectness:* The RCT studies directly compared the effect of GLP-1 RA with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms. One study was an active comparator trial with comparable glycemic and blood pressure control between GLP-1 RA– and insulin-treated groups.
- *Precision:* For critical and important outcomes, the precision is good, as the studies conducted included large numbers of study participants with acceptable event rates. However, in participants with CKD and diabetes, there were fewer events, and some outcomes (AKI and hyperkalemia) did not exclude minimally clinical important difference. Hence, these outcomes have been downgraded due to serious imprecision.
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. The majority of studies were commercially funded, but overall, there was no evidence of undue industry influence on the included RCT findings.

Values and preferences. The Work Group judged that the majority of well-informed patients with T2D and CKD who cannot take an SGLT2i because of intolerance or a contraindication would choose to receive a GLP-1 RA because of the cardiovascular benefits associated with this class of medications. Patients at high risk for ASCVD or with residual albuminuria who need further glycemic management might be particularly inclined to choose a GLP-1 RA. In contrast, patients who experience severe gastrointestinal side effects or are unable to administer an injectable medication, or those for whom GLP-1 RA are unaffordable or unavailable, will be less inclined to choose these agents.

Resource use and costs. Although some models have found the use of GLP-1 RA to be a cost-effective strategy among patients with T2D,[397,398] these medications are frequently cost-prohibitive for many patients compared to other oral glucose-lowering agents (e.g., sulfonylureas), which do not have evidence for cardiovascular and kidney benefits. In many cases in the US, obtaining preauthorization from insurance companies for GLP-1 RA places an undue burden on healthcare professionals and patients. Even with insurance coverage, many patients are still faced with a large copayment.

Availability of drugs also varies among countries and regions. Thus, treatment decisions must take into account the patient's preference, drug availability in the country, and cost. Ultimately, patients may need to choose between the cost of these medications versus their anticipated benefits, and some patients may not be able to access them.

Considerations for implementation. For patients with T2D and CKD, the Work Group recommends prioritizing, after lifestyle measures, metformin and an SGLT2i as initial glucose-lowering medications. For patients unable to take or tolerate these medications, or if additional glycemic management is needed, these guidelines then recommend prioritizing GLP-1 RA over other glucose-lowering agents, given their established cardiovascular and potential kidney benefits (Figure 23). This approach is consistent with the recommendations from other professional societies, including the ACC,[142] ADA,[145,147] and ESC/EASD.[144]

Patients with T2D and CKD benefited from GLP-1 RA therapy in RCTs. In subgroup analysis from the conducted trials of GLP-1 RA therapy in patients with T2D and CKD, the cardiovascular benefits were sustained, independent of age, sex, and race/ethnicity. Thus, this recommendation holds for all patients. However, long-term follow-up and ongoing collection of real-world data are needed to validate effectiveness and potential harms.

This recommendation applies to kidney transplant recipients, as there is no evidence to indicate different outcomes in this population. Conversely, there is less available safety data for patients with CKD G5 or on kidney replacement therapy, so caution should be exercised in these groups.[399] These medications may exacerbate gastrointestinal symptoms in peritoneal dialysis patients or those who are uremic or underdialyzed, or those who have cachexia or malnutrition.

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

When the decision has been made to add a GLP-1 RA, given that the ELIXA (lixisenatide),[381] and EXSCEL (exenatide)[376,378] trials did not prove cardiovascular benefit with these agents, and that albiglutide and efpeglenatide are

currently unavailable, the priority is to use one of the other GLP-1 RA, which have proven cardiovascular and kidney benefit (i.e., liraglutide, semaglutide [injectable], and dulaglutide). Additionally, cardiovascular benefit has not been demonstrated for oral semaglutide, as the PIONEER 6[383] trial was powered for only non-inferiority, although a larger outcome cardiovascular trial for oral semaglutide is ongoing (SOUL, NCT03914326).

Patients with T2D and CKD are a heterogeneous group of patients, and treatment of hyperglycemia is complex. Treatment algorithms must be tailored to individuals, taking into consideration patient priorities and preferences, treatment availability, and cost, as part of shared decision-making.

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 29).

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

DPP-4 inhibitors and GLP-1 RA should not be used together. Given that GLP-1 RA have been shown to have cardiovascular benefit, consideration may be given to stopping the gliptin medication (DPP-4) in order to facilitate treatment with a GLP-1 RA instead.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

GLP-1 RA are preferred over classes of glucose-lowering medications with less evidence supporting reduction of cardiovascular or kidney risks (e.g., DPP-4 inhibitors, thiazolidinediones, sulfonylureas, insulin, and acarbose). GLP-1 RA on their own do not cause hypoglycemia, but they may increase the risk of hypoglycemia caused by sulfonylureas or insulin when used concurrently. Therefore, it is reasonable to stop or reduce the dose of sulfonylurea or insulin when starting a GLP-1 RA if the combination may lead to an unacceptable risk of hypoglycemia.

Practice Point 4.2.5: GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

Persons with T2D and CKD often are obese even at advanced stages of CKD. Obesity has numerous adverse health effects, including higher risks of CVD and CKD. These risks are mediated by "indirect" effects such as worsened risk factors (e.g., hyperglycemia, hypertension) as well as by "direct" effects of obesity (e.g., pro-inflammatory state, fat compression of organs).[400,401] As a class, GLP-1 RA have demonstrated weight-loss effects. Both semaglutide and liraglutide have been studied and approved for weight loss in nondiabetic obesity.[402] In addition, tirzepatide has also been studied for obesity in patients without diabetes in the A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMONT) trial. In the AWARD-7 trial of patients with T2D and CKD G3a–G4, dulaglutide treatment (1.5 mg weekly) produced a mean weight loss of nearly 4 kg over 1 year, while insulin users gained >1 kg on average.[382] Thus, the weight differential between conventional insulin and dulaglutide treatment was about 5 kg after 1 year. This magnitude of weight loss is clinically meaningful from the perspectives of improving cardiovascular and CKD risk factors and for kidney and heart protection. Furthermore, weight loss may be required to qualify people with obesity and advanced stages of CKD for kidney transplant. GLP-1 RA promotes weight loss in these

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 μg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 μg and 20 μg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Figure 29| Dosing for available glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dose modification for chronic kidney disease (CKD). CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate.

individuals and can be a valuable tool to increase rates of preemptive and overall kidney transplants.

Research recommendations

- Future GLP-1 RA studies should consider evaluating kidney outcomes as the primary outcome.
- Future evidence should confirm clinical evidence of cardiovascular outcome and kidney benefit of GLP-1 RA among patients with T2D in a population selected for CKD, as prior studies have examined only CKD subgroups enrolled in the main trials.
- Future studies should focus on long-term (>5 years) safety and efficacy of using GLP-1 RA among patients with T2D and CKD. We need continued longer safety follow-up data and post-marketing surveillance including real-world evidence studies.
- Future studies should confirm the safety and clinical benefit of GLP-1 RA for patients with T2D with severe CKD, including those who are on dialysis, for whom there are limited data, and provide more data on CKD G4.
- Future studies should confirm the safety and clinical benefit of GLP-1 RA for patients with T2D and kidney transplant.
- Future studies should examine what biomarkers are appropriate to follow to assess the clinical benefit of GLP-1 RA (i.e., HbA1c, body weight, blood pressure, albuminuria, etc.).
- Although the REWIND trial provided encouraging results about the cardiovascular outcome benefit of GLP-1 RA among patients with T2D and CKD without established CVD (i.e., exclusively primary prevention population), more population or trial data would be useful to confirm their role, as most studies have focused on secondary prevention.
- Future studies should focus on kidney and heart protective benefits of GLP-1 RA, as well as their safety, for use in patients with T1D.
- Future studies should examine whether there are safety and efficacy issues of GLP-1 RA among individuals with a history of T2D and CKD who now have controlled HbA1c <6.5%. For example, among CKD patients at high risk for ASCVD, is there a benefit to using GLP-1 RA among individuals who currently have good glycemic control?
- Future studies are needed on the efficacy and safety of the newly FDA-approved tirzepatide in patients with diabetes and CKD. The dual agonists, glucose-dependent insulinotropic peptide-glucagon-like peptide 1 (GIP/GLP-1), are emerging as an additional therapeutic option, but currently, data are limited in this population.
- Future studies should report on the cost-effectiveness of this strategy that prioritizes adding a GLP-1 RA as a second-line pharmacologic agent, after metformin and an SGLT2i, among patients with T2D and CKD, rather than other antiglycemic medications, while factoring in cardiovascular and kidney benefits against the cost of medications and the potential for adverse effects.
- Future studies should further investigate whether the cardiovascular and kidney benefits are increased when GLP-1 RA are combined with SGLT2i treatment.
- Future work should address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake in low-resource settings.

Chapter 5: Approaches to management of patients with diabetes and CKD

5.1 Self-management education programs

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (Figure 30[403]) *(1C)*.

This recommendation places a high value on the potential benefits of structured education programs in people with diabetes and CKD, especially when implemented according to the chronic care model (see Section 5.2: Team-based integrated care). The recommendation also places a relatively high value on the potential for such programs to enable the delivery of evidence-based care. The recommendation places a relatively lower value on the lack of high-quality evidence supporting clinically relevant benefits of such programs, specifically in people with diabetes and CKD. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. Diabetes self-management education programs are guided by learning and behavior-change theories, are tailored to a person's needs, and take into account ethnic, cultural, literacy, cognitive, and geographic factors.[403] The overall objective of self-management programs is to empower and enable individuals to develop self-management knowledge and skills with the aim of reducing the risk of long-term microvascular and macrovascular complications, severe hypoglycemia, and diabetic ketoacidosis. Self-management programs also seek to optimize patient well-being, improve quality of life, and achieve treatment satisfaction.[403]

Potential benefits are summarized in a systematic review of 21 studies (26 publications, 2833 participants), which showed that group-based diabetes self-management education programs in people with T2D result in improvements in clinical outcomes (HbA1c, fasting glucose), body weight, and psychosocial outcomes (diabetes self-knowledge, self-efficacy, self-management skills, patient satisfaction).[404] The best approach is tailored to individual preferences and learning styles.[403]

Lifestyle management, including medical nutrition therapy, physical activity, weight loss, counseling for smoking cessation, and psychological support is often delivered in the context of diabetes. Self-management education and support are fundamental aspects of diabetes care. Self-management programs delivered from diagnosis can promote medication adherence, healthy eating, physical activity, and psychological well-being, and increase self-efficacy. The best outcomes are achieved in those programs with a theory-based and structured curriculum and with a contact time of more than 10 hours with a patient-centered philosophy. Although online programs may reinforce learning, there is little evidence to date that they are effective when used alone.[405]

There is no expected or anticipated harm to patients if diabetes self-management and education support (DSMES)

Figure 30 | Key objectives of effective diabetes self-management education programs. Reprinted from *The Lancet Diabetes & Endocrinology*, volume 6, Chatterjee S, Davies MJ, Heller S, Speight J, Snoek FJ, Khunti K. Diabetes structured self-management education programmes: a narrative review and current innovations, pages 130–142, Copyright © 2018, with permission from Elsevier.[403]

programs are commissioned and delivered according to evidenced-based guidelines. When self-management programs are not conducted in a structured and monitored way, there is a risk for inefficient programs with a low cost–benefit ratio. Otherwise, there is usually not considered to be any harm related to education in self-management.

The key components of self-management education recommended by the United Kingdom National Clinical Institute for Care and Excellence (NICE) guidelines can be outlined as follows:

- is evidence-based;
- is individualized to the needs of the person, including language and culture;
- has a structured theory-driven written curriculum with supporting materials;
- is delivered by trained and competent individuals (educators) who are quality-assured;
- is delivered in group or individual settings;
- aligns with the local population needs;
- supports patients and their families in developing attitudes, beliefs, knowledge, and skills to self-manage diabetes;
- includes core content (i.e., diabetes pathophysiology and treatment options; medication usage; monitoring, preventing, detecting, and treating acute and chronic complications; healthy coping with psychological issues and concerns; problem-solving and dealing with special situations [e.g., travel, fasting]);
- is available to patients at critical times (i.e., at diagnosis, annually, when complications arise, and when transitions in care occur);
- includes monitoring of patient progress, including health status, and quality of life; and
- has a quality assurance program.

Quality of evidence. Overall, the quality of the evidence was low because many critical and important outcomes were not reported, and surrogate outcomes exhibited low quality of evidence.

The evidence review included RCTs that focused on educational programs in patients with diabetes and CKD to prevent the progression of CKD, improve diabetic control, and improve quality of life. The review identified 2 RCTs that compared self-management education programs (specialist dietary advice) with multifactorial care in patients with diabetes and CKD (Supplementary Table S24[406–408]). Only surrogate outcomes were reported, and the quality of the evidence was rated as low due to the very serious risk of bias (lack of blinding of outcome assessors, high numbers lost to follow-up). Additionally, the evidence review identified 1 RCT that compared self-management education programs plus routine treatment with routine treatment alone (Supplementary Table S25[408-411]). This study exhibited low quality of the evidence for the self-efficacy because of study limitations such as inadequate randomization sequence generation and lack of blinding of study personnel and participants.

A systematic review of RCTs published in 2018 on self-management support interventions in people with CKD[412] was rated as a high-quality review according to the systematic review critical appraisal tool A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2).[413] The systematic review and meta-analysis of 8 studies identified moderate quality of the evidence for self-management activation and medication adherence outcomes (Supplementary Table S26[412]; Figures 31[412] and 32[409,412,414–420]) The quality of the evidence was downgraded for self-management activation because of heterogeneity ($I^2 = 63\%$), and medication adherence was downgraded because of a reliance on self-report (indirectness). Other surrogate outcomes, such as blood pressure and HbA1c, were downgraded to low because of lack of blinding of study personnel, participants, and outcome assessors, and a lack of allocation concealment.

Additionally, other studies on self-management support in patients with CKD identified by the Work Group were observational studies and exhibited bias by design,[421] or in 1 case was a small RCT[422] with various study limitations, and hence the quality of the evidence was low.

Values and preferences. The Work Group judged that diverse self-management education programs allow for informed decision-making and support. These include face-to-face, group-based, or digital self-management programs. In addition, the Work Group judged that patients would value having the programs be available and delivered in languages appropriate for the healthcare setting and taking into account the values, preferences, and cultural context of people with diabetes and CKD. The recommendation is strong, as the Work Group felt that all or nearly all well-informed patients would choose self-management as the cornerstone of any chronic care model. The recommendation places a high value on the potential benefits of structured education programs in people with diabetes and CKD, especially if implemented according to the chronic care model (see Section 5.2: Team-based integrated care). The recommendation also places a relatively high value on the potential for such programs to enable the delivery of evidence-based care. The recommendation places a relatively lower value on the lack of high-quality evidence supporting clinically relevant benefits of such programs in people with diabetes and CKD specifically.

Resource use and costs. Diabetes self-management education programs can vary in terms of intensity, mode of delivery, reach, effectiveness, and cost-effectiveness. One recent systematic review of 8 RCTs concluded that the reduction of clinical risk factors in self-management education programs is likely to be cost-effective in the long-term.[412] Another review of 22 studies suggested that self-management education programs are more cost-effective than or superior to usual care. The review also found that telemedical methods of delivering programs were potentially not cost-effective.[423] One review of 26 studies describing cost-effectiveness of self-management education in T1D and T2D identified that over half of self-management approaches were associated with

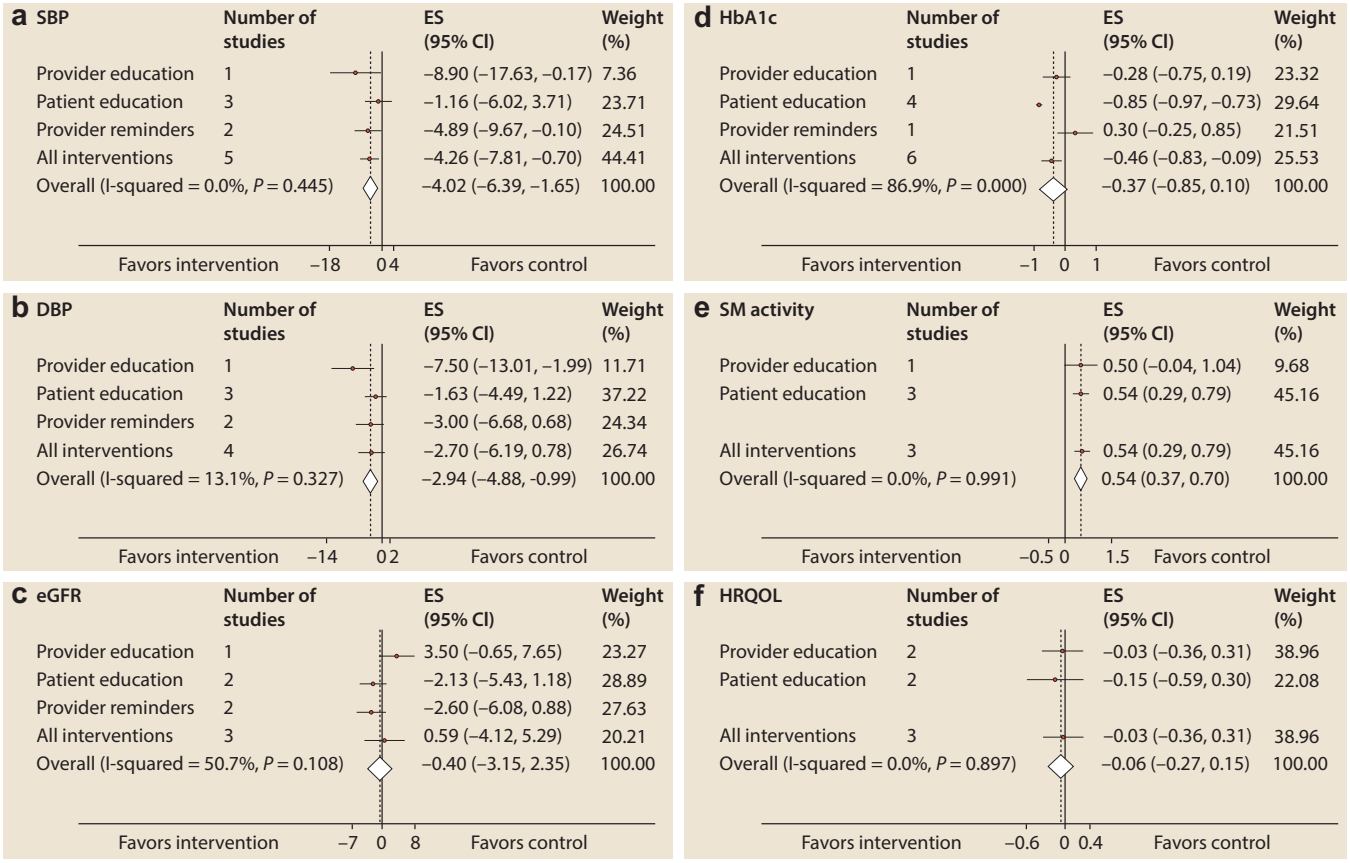


Figure 31 | Meta-analysis showing the effect of different intervention components on (a) systolic blood pressure (SBP), (b) diastolic blood pressure (DBP), (c) estimated glomerular filtration rate (eGFR), (d) glycated hemoglobin (HbA1c; %), (e) self-management (SM) activity, and (f) health-related quality of life (HRQOL). CI, confidence interval; ES, effect size. Reproduced from Zimbudzi E, Lo C, Misso ML, et al. Effectiveness of self-management support interventions for people with comorbid diabetes and chronic kidney disease: a systematic review and meta-analysis. *Syst Rev.* 2018;7:84.[412] Copyright © The Authors, http://creativecommons.org/licenses/by/4.0/.

cost-savings, cost-effectiveness, reduced cost, or positive investment returns.[424]

Considerations for implementation. Healthcare organizations need to have a trained workforce to deliver self-management programs for people with diabetes and CKD. There is very little evidence on specific self-management programs for people with different severities of CKD and in people of different ethnic minority groups. Healthcare organizations need to be aware of these limitations and consider developing and evaluating programs that are tailored to their local populations. Several definitions have been proposed to define self-management education programs. The ADA defines diabetes self-management education as the ongoing process of facilitating knowledge, skills, and abilities necessary for diabetes self-care, incorporating a person-centered approach, and shared decision-making.[309] NICE defines self-management education as an evidence-based structured curriculum defining specific aims and objectives delivered by trained educators.[403] NICE also recommends that the programs be quality-assured and audited against consistent criteria by independent assessors.[425,426] NICE recommends that a multidisciplinary team that includes at least 1 trained or accredited healthcare practitioner, such as a diabetes specialist nurse or registered dietitian, deliver the program, either one-on-one or in groups that may be combined with support via telephone or web-based platforms. NICE recommends that self-management education be offered to people with diabetes at diagnosis, with ongoing maintenance sessions.[426]

Rationale

In the judgment of the Work Group, diabetes self-management education programs should be individualized and tailored to the changing biomedical and psychosocial needs of the person with T1D or T2D. Diabetes self-management education can be provided in a number of formats, such as one-on-one education, group-based sessions, or via telemedicine, and can be delivered by different members of healthcare teams.

Practice Point 5.1.1: Healthcare systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.

Diabetes self-management education programs should be individualized and tailored to the changing biomedical and psychosocial needs of the person with diabetes. Globally, there are major gaps in the implementation of self-management

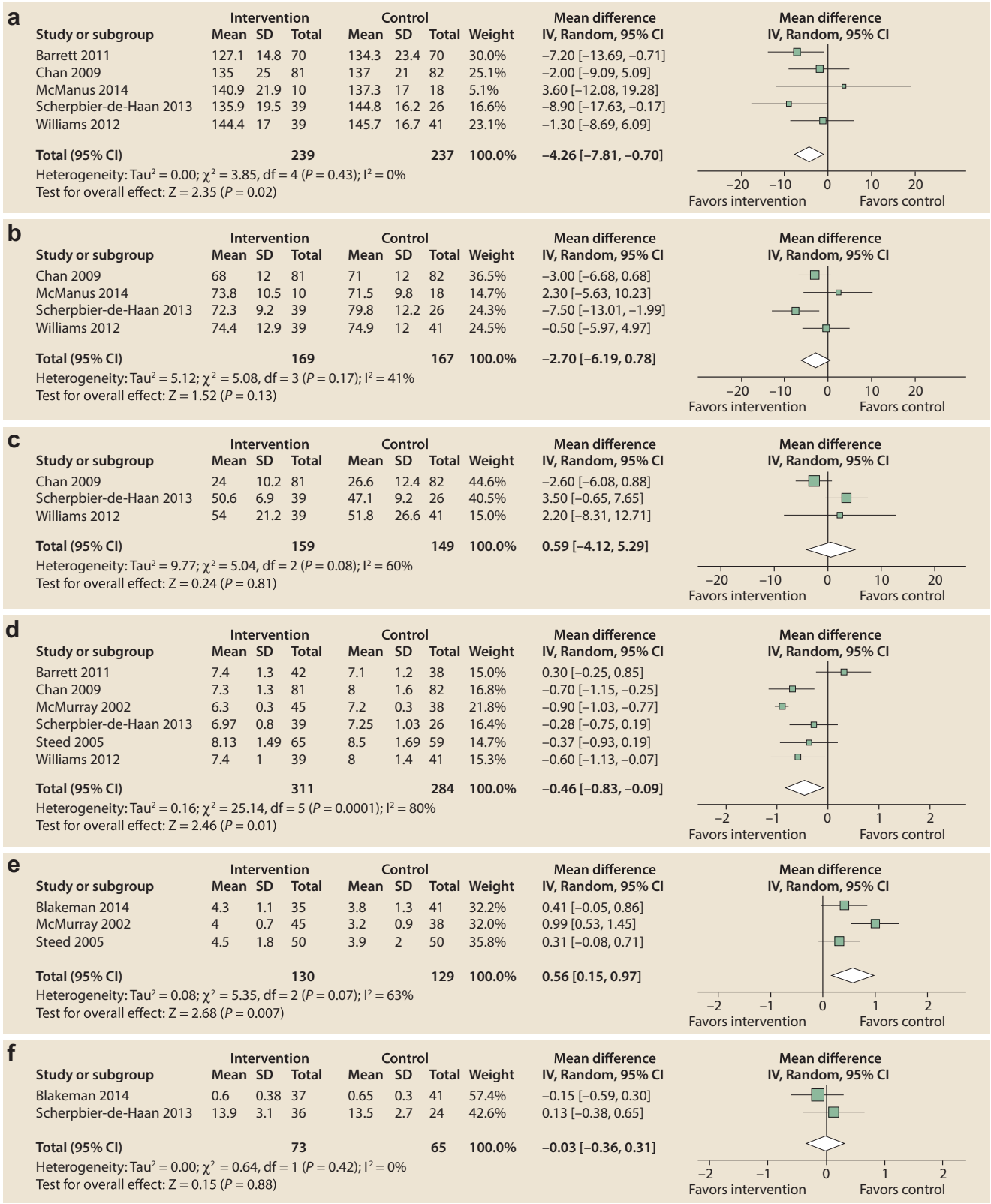


Figure 32| Forest plots showing outcomes for people with diabetes and chronic kidney disease (CKD) undergoing self-management (SM) education programs.[409,412,414–420] (a) Systolic blood pressure (SBP), (b) diastolic blood pressure (DBP), (c) estimated glomerular filtration rate (eGFR), (d) glycated hemoglobin (HbA1c; %), (e) SM activity, and (f) health-related quality of life (HRQOL). CI, confidence interval; df, degrees of freedom; IV, inverse variance. Reproduced from Zimbudzi E, Lo C, Misso ML, et al. Effectiveness of self-management support interventions for people with comorbid diabetes and chronic kidney disease: a systematic review and meta-analysis. *Syst Rev.* 2018;7:84.[412]

education programs, and many do not meet criteria set for self-management programs, including an evidence-based structured curriculum delivered by trained educators and quality assurance of the program. Diabetes self-management programs can be delivered face-to-face, as one-to-one or group-based programs, or via technology platforms by different members of healthcare teams, depending on the availability in the healthcare setting.

Research recommendations

- There is a lack of specific self-management education programs with proven effectiveness and cost-effectiveness for people with CKD. Future studies are needed to determine the effectiveness of these programs in multiethnic populations.
- Most evaluations have been of short-term programs, and future studies should include evaluations of longer-term self-management programs.
- Novel methods of delivering the self-management programs, including those delivered using technologies and one-on-one or group-based interactions, should be pursued and evaluated.
- There is a lack of uptake of self-management programs even when they are available in a universal health system such as that in the UK.[427,428] Hence, further research should address methods of engagement and longer-term retention within programs.
- Future evaluations of self-management programs should include assessment of duration, frequency of contacts, methods of delivery, and content.
- Many minority ethnic groups have a higher prevalence of diabetes and its associated complications (e.g., migrant South Asian and Hispanic populations in the US). Self-management education programs often are not culturally tailored to suit minority populations. However, culturally adapted programs may be effective, especially if delivered with community support.[422] Given these findings, what are the key elements of a successful program that targets specific ethnic or minority populations?

5.2 Team-based integrated care

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD *(2B)*.

This recommendation places a relatively higher value on the potential benefits of multidisciplinary integrated care to improve outcomes, self-management, and patient–provider communication in patients with diabetes and CKD (Figure 33[429–432]). The recommendation places a relatively lower value on challenges related to implementing such care across diverse clinical settings, requiring system support and policy change. The recommendation also places a relatively lower value on the lack of high-quality evidence demonstrating that such care improves clinically relevant outcomes in people with diabetes and CKD specifically. This recommendation applies to patients with T1D or T2D.

Key information

Balance of benefits and harms. Individuals with diabetes and CKD have complex phenotypes including multiple risk factors and complications. Due to altered kidney function, these individuals are also at high risk of developing hypoglycemia and adverse drug reactions. The multiple lifestyle factors, notably diet and exercise, as well as psychosocial factors, can influence behaviors, including medication nonadherence, with poor outcomes.[4,433–435] These clinical needs call for a change in care delivery in order to stratify risk, triage care, empower patients, and support decision-making in a timely manner. Given the large number of patients and comparatively few healthcare providers and the silent nature of risk factors and complications, there is a strong rationale to leverage the complementary knowledge, skills, and experiences of physician and nonphysician personnel (see Practice Point 5.2.1), and to use a team-based and integrated approach to manage these patients, focusing on regular assessment, control of multiple risk factors, and self-management to protect kidney function and reduce risk of complications.[429,436]

Systematic reviews and meta-analyses support the benefits of multicomponent integrated care targeted at systems, patients, and care providers in reducing multiple cardiometabolic risk factors in T2D.[403,437,438] In a meta-analysis of 181 trials of various quality-improvement strategies, patient education with self-management, task-shifting, and use of technology or nonphysician personnel to promote patient–healthcare provider communication had the largest effect size, especially in low-resource settings. In 12 of these trials, hypoglycemia was a study outcome, with 9 trials indicating no between-group difference; 2 trials showed a reduction in hypoglycemia with intervention, and 1 trial increased non-severe hypoglycemic events with intervention, although the rate was very low, with no severe hypoglycemia.[437]

Quality of evidence. The overall quality of the evidence was rated as moderate, due to indirectness, because of the reliance on studies from the general diabetes population. The ERT completed a systematic review examining RCTs that compared models of care for the management of patients with diabetes and CKD. RCTs that compared specialist-led multidisciplinary, multicomponent integrated care for treating multiple targets versus standard care exhibited moderate quality of the evidence for critical outcomes, including kidney failure, systolic blood pressure level, and HbA1c level (Supplementary Table S27).[406] Trials that compared the addition of exercise advice and supervision,[439] exercise and diet,[439] or self-monitoring and medicine reviewing, educational DVD (digital video disc), and follow-up calls to standard care did not report on critical and important outcomes stipulated in this guideline.[440]

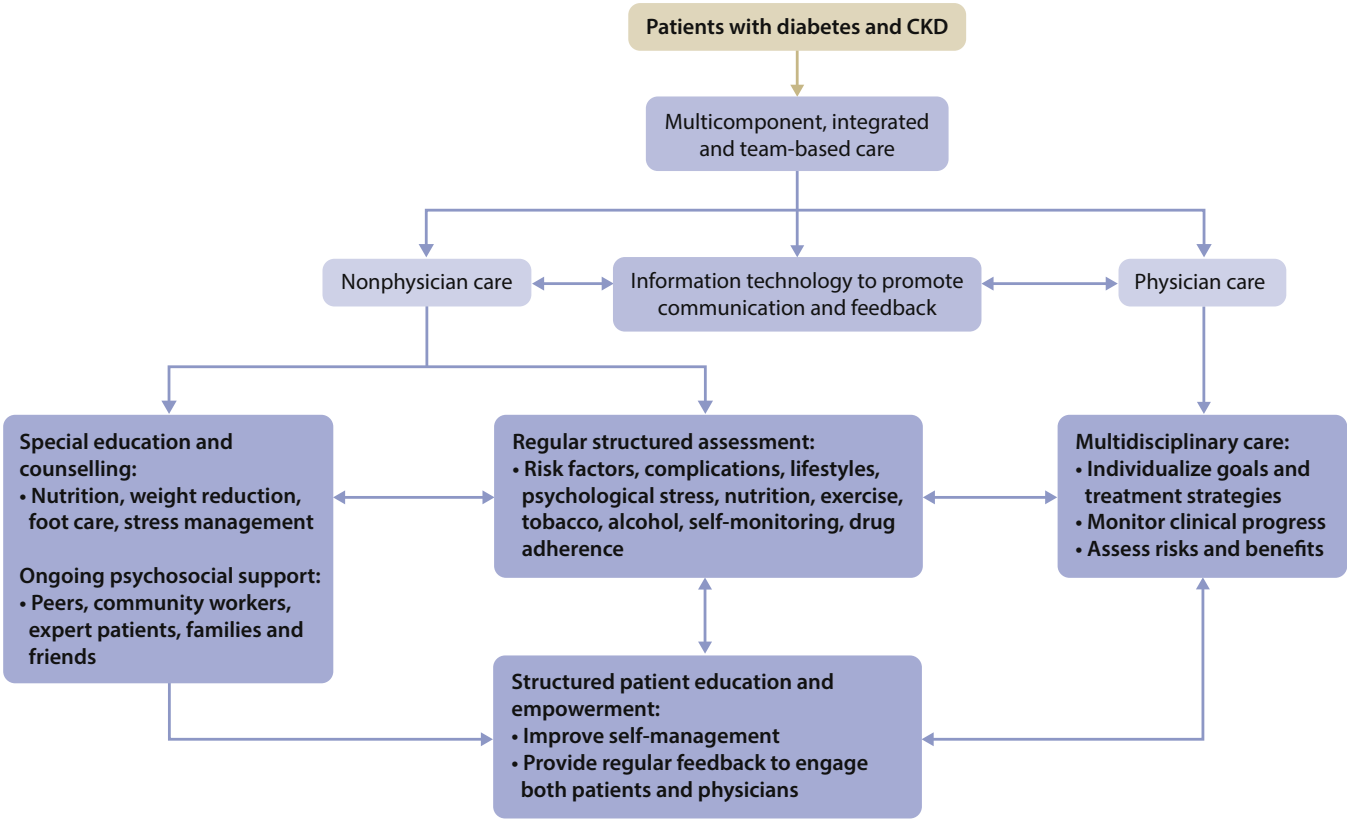


Figure 33 | Integrated care approach to improve outcomes, self-management, and patient–provider communication in patients with diabetes and chronic kidney disease (CKD).[429–432] A schematic diagram showing the use of physician and nonphysician personnel to provide regular assessments, assisted by information technology, to facilitate individualized management and patient self-management with ongoing support in order to detect, monitor, and treat risk factors and complications early to reduce hospitalizations, multiple morbidities, and premature death.

A published systematic review, comparing multicomponent integrated care lasting for at least 12 months with standard care in patients with diabetes, exhibited moderate quality of the evidence (Supplementary Table S28).[437] The quality of the evidence was rated as moderate because of indirectness, as the review population (patients with diabetes) was different from the population of interest (patients with CKD and diabetes) in this guideline. However, some of the studies included in this review included patients with CKD, with kidney failure as a study outcome measure.[415]

Values and preferences. In the judgment of the Work Group, healthcare providers need an optimal work environment and support system with appropriate infrastructures, facilities, and tools to assess clinical needs and individualize care plans in order to bring out the best of clinical expertise and medical technologies.[441] Apart from medical care, patients with diabetes with or without CKD may need advice, every now and then, from allied healthcare professionals, such as nurse educators, registered dietitians, physical trainers, social workers, psychologists, or pharmacists on how to cope with the condition on a daily basis.[442] In some patients with T2D, especially those with social disparity or emotional distress, psychosocial support from peers[443] and community healthcare workers[444] can also improve metabolic control and emotional well-being, and reduce hospitalizations.

In the judgment of the Work Group, meeting these pluralistic needs of patients with diabetes and CKD requires a diversity of knowledge, skills, and experiences that can be achieved only through team-based management. This care model may incur upfront investment needed to build capacity, retrain/redeploy staff, re-engineer workflow, and intensify ambulatory care, including use of medications, which may lead to opportunity costs for intervention for other diseases. Overtreatment, especially with insufficient monitoring, may also lead to adverse events such as hypoglycemia, hypotension, or drug–drug interactions. However, given the multiple morbidities associated with diabetes, the high costs of cardiovascular–kidney complications, notably kidney failure,[445] and the proven benefits of control of cardiometabolic and lifestyle risk factors on these outcomes,[8,429,446] the Work Group judged that this upfront investment is likely to translate into long-term benefits.

Resource use and costs. In a 2-year RCT, patients with T2D and CKD who received team-based structured care were more likely to achieve multiple treatment targets, compared to those who received usual care. Patients who attained multiple treatment targets had a more than 50% reduced risk of cardiovascular–kidney events and all-cause death compared with those with suboptimal control.[415] In an RCT lasting for 7.8 years, high-risk patients with T2D and moderately

increased albuminuria who received team-based multifactorial care had a 50% reduced risk of cardiovascular events compared to those receiving usual care.[9] These benefits translated to reduced hospitalization rates and a gain of 7.9 years of life after 20 years.[8] Both of these team-based care models in patients with T2D and CKD focusing on treatment with multiple targets and self-management were found to be cost-effective and cost-saving, if implemented in the primary care setting.[447,448]

Considerations for implementation. This recommendation recognizes potential resource constraints and insufficient capacity in delivering team-based care, especially in some low-income and middle-income countries. However, it is also these countries that often have the fewest resources to provide expensive care for advanced disease, making prevention through care reorganization and patient education using a "train the trainer" approach an important strategy to prevent the onset and progression of complications such as CKD. In high-income countries, system and financial barriers often make delivery of quality diabetes/kidney care suboptimal, which means policymakers, planners, and payers need to build capacity, strengthen the system, and reward preventive care to enable the delivery of evidence-based and value-added care for better outcomes.[430,449]

Rationale

Patients with diabetes and CKD have an 8-fold higher risk of cardiovascular and all-cause mortality compared to those without diabetes and CKD.[450] Control of blood glucose, blood pressure, and blood cholesterol, as well as the use of RASi and statins, have been shown to reduce the risk of cardiovascular–kidney disease.[4] However, in real-world practice, there are considerable care gaps in low-income, middle-income,[451] and high-income countries.[452] This care gap is often due to lack of timely and personalized information needed to motivate self-care, guide treatment strategies, and reinforce adherence to medications.[429,434] Although self-care represents a cornerstone of diabetes management, there is also a need to take cultures, preferences, and values into consideration in order to individualize diabetes education and promote adherence.[403]

Care organization, informed patients, and proactive care teams form the pillars of the chronic care model aimed at promoting self-management and shared decision-making (Figure 34).[436] The concept of a chronic care model focusing on team management, data collection, and care integration is analogous to the protocol-driven care in clinical trial settings in which care coordination, treatment adherence, and monitoring by nonphysician staff are key to successful implementation. In these structured care settings, trial participants often had considerably lower event rates than their peers with similar or lower risk profiles managed in real-world practice.[453,454] Therefore, despite the relative lack of direct evidence, the Work Group judged that multidisciplinary integrated care for patients with diabetes and CKD would represent a good investment for health systems. In the judgment of the Work Group, most well-informed policymakers would choose to adopt such models of care for this population, providing that resources were potentially available.

Despite the potential value of these chronic care models, there are major implementation gaps due to factors pertinent

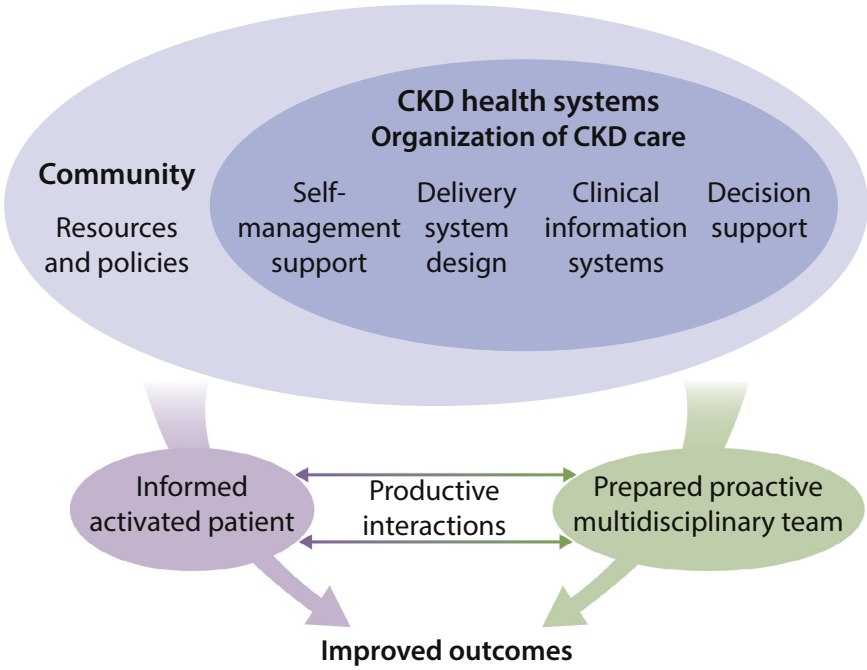


Figure 34| The chronic care model. The chronic care model emphasizes the additive benefits of different components at the system, policy, provider, and patient levels in improving clinical outcomes. CKD, chronic kidney disease. Reproduced from Improving the quality of health care for chronic conditions, Epping-Jordan JE, Pruitt SD, Bengoa R, et al., volume 13, 299–305, Copyright © 2004, with permission from BMJ Publishing Group Ltd.[436]

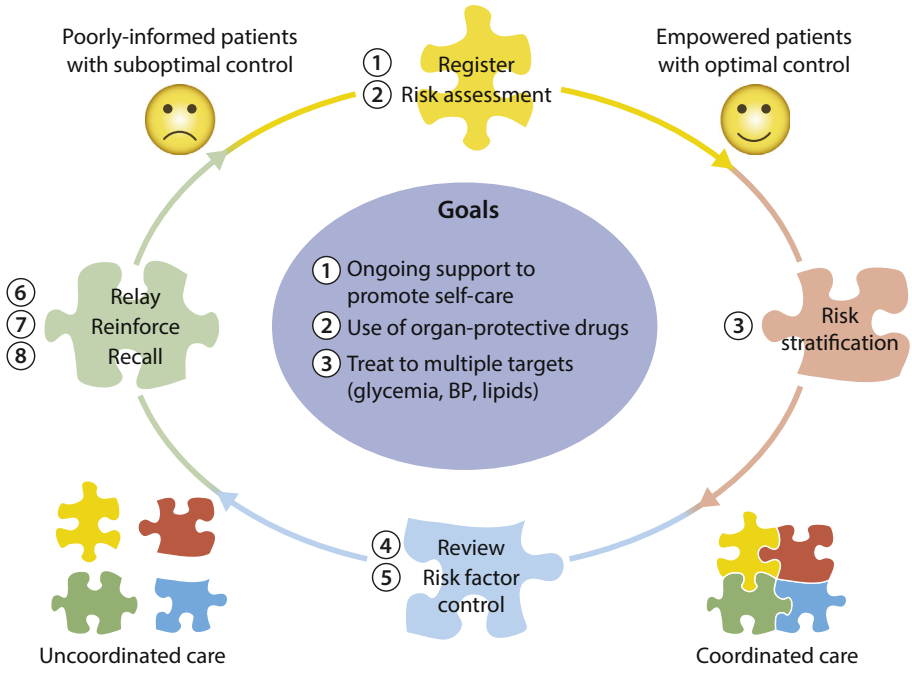


Figure 35 | Team-based integrated care delivered by physicians and nonphysician personnel supported by decision-makers. BP, blood pressure.

to patients (e.g., motivation, adherence, support), systems (e.g., information, infrastructure, capacity), and healthcare providers (e.g., knowledge, skills, incentives). The relative importance of these factors is often context-specific and may vary among and within countries, as well as over time, depending on socioeconomic development and healthcare provision (single or multiple care providers; public, private, or subsidized), and payment (social or private insurance) policies.

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, healthcare assistants, community workers, and peer supporters) preferably with knowledge of CKD (Figure 35).

Decision-makers allocate or redistribute resources, supported by appropriate policies, to facilitate the formation of a multidisciplinary team including physicians and nonphysician personnel to deliver structured care in order to stratify risk, identify needs, and individualize targets and treatment strategies. Greater communication and more closely coordinated care among different specialties (e.g., cardiology, endocrinology, nephrology, primary care) and other allied health professionals should be a key pillar of this team-based integrated care. We envision that this approach can help deliver the multifaceted strategies set forth in this guideline, and we emphasize that these recommendations and practice points should be viewed collectively as key components for general holistic management of patients with CKD and diabetes. Within team-based structured care, practitioners should define care processes and re-engineer workflow, supported by an information system with decision support, to deliver team-based structured care that should consist of the following steps:

- Establish a register by performing comprehensive risk assessment, including blood/urine and eye/foot examination every 12–18 months, as recommended by practice guidelines.
- Assess cardiometabolic risk factors (e.g., blood pressure, glycated hemoglobin, body weight) every 2–3 months.
- Assess kidney function (e.g., eGFR and ACR) every 3–12 months.
- Review treatment targets and use of organ-protective medications at each visit.
- Reinforce self-management (e.g., self-monitoring of blood pressure, blood glucose, body weight) and identify special needs at each visit.
- Provide counseling on diet, exercise, and self-monitoring with ongoing support, and recall defaulters at the clinic visit.

Administrators or managers should conduct periodic audits on a system level to identify care gaps and provide feedback to practitioners with support to improve the quality of care.

Research recommendation

- There is a need for funding agencies to support implementation research or naturalistic experiments to evaluate context-relevant, team-based integrated care, taking into consideration local settings, cultures, and resources in order to inform practices and policies.

Methods for guideline development

Aim

The aim of this project was to update the evidence-based clinical practice guideline for the monitoring, prevention of disease progression, and treatment in patients with diabetes and CKD published in 2020.[155] The guideline development methods are described below.

Overview of process

These guidelines adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3),[455,456] and have been reported in accordance with the Appraisal of Guidelines for Research and Evaluation (AGREE) II reporting checklist.[457] The processes undertaken for the development of the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD* are described below.

- Defining the scope of the guideline update
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the literature
- Updating the evidence synthesis and meta-analysis to include newly identified studies
- Updating the quality of the evidence for each outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the quality of the evidence and other considerations
- Convening a public review of the guideline draft in February 2022
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT for the guideline update. For the guideline update, the previously assembled Work Group with expertise in adult nephrology, cardiology, endocrinology, dietetics, epidemiology, primary care, and public health, as well as people living with diabetes and kidney disease were engaged. Cochrane Kidney and Transplant, with expertise in adult and pediatric nephrology, evidence synthesis, and guideline development, was again contracted as the ERT tasked with updating the systematic evidence review. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the quality of the evidence per outcome, and grading the quality of the evidence for the recommendations. The Work Group was responsible for writing the graded recommendations and the underlying rationale, grading the strength of the recommendations, and developing practice points.

Defining scope and topics for the guideline update. Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to RCTs. Guideline topics and clinical questions focusing on non-randomized studies were not included in the guideline update (Supplementary Table S1). For efficiency and prioritization of the guideline update, the Work Group identified key questions that were known to be addressed by newly published RCTs. Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. Details of the Population, Intervention, Comparator, Outcome (list of critical and important outcomes detailed in Table 1), and Methods (PICOM) questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.[15,129,168,250,325,408,458–462] All evidence reviews were conducted in accordance with the Cochrane Handbook,[463] and guideline development adhered to the standards of GRADE (Grading of Recommendation, Assessment, Development, and Evaluation).[464]

Literature search and article selection. Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. The Cochrane Kidney and Transplant Registry of

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Cardiovascular mortality • Kidney failure • 3-point and 4-point MACE • Individual cardiovascular events (myocardial infarction, stroke, heart failure) • Doubling of serum creatinine • Hypoglycemia requiring third-party assistance • Attaining HbA1c • Change in HbA1c • Hyperkalemia
Important outcomes	• Albuminuria progression (onset of albuminuria, moderately increased to severely increased albuminuria)
Non-important outcomes	• eGFR/creatinine clearance

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MACE, major cardiovascular events.

Table 2 | Clinical questions and systematic review topics in the PICOM format

Guideline chapter 1	Comprehensive care in patients with diabetes and CKD
Clinical question	**Do RAS inhibitors improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	ACEi and ARB
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Strippoli *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev.* 2006;CD006257.[15]
SoF tables	Supplementary Tables S4, S5, S29, S30, and S34
Clinical question	**Does dual RAS inhibition compared to mono RAS inhibition improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Dual RAS inhibition (ACEi and ARB)
Comparator	Mono RAS inhibition (ACEi or ARB)
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Strippoli *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev.* 2006;CD006257.[15]
SoF tables	Supplementary Table S31
Clinical question	**In patients with T2D and CKD, what are the effects of SGLT2i on clinically relevant outcomes and clinically relevant harms?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T2D)
Intervention	SGLT2i
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Long-term harms: hypoglycemia, lactic acidosis, amputation, bone fractures
Study design	RCT Long-term harms: systematic review of observational studies
Cochrane systematic reviews	Lo *et al.* Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev.* 2018;9:CD011798.[129] Lo *et al.* Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev.* 2017;2:CD009966.[459]
SoF tables	Supplementary Tables S6, S32, S33
Clinical question	**Does the addition of medication blocking the action of aldosterone on RAS compared to standard of care or RAS inhibition alone improve clinically important outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Mineralocorticoid receptor antagonists or direct renin inhibitors
Comparator	Standard of care or RAS inhibition
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Andad *et al.* Direct renin inhibitors for preventing the progression of diabetic kidney disease (protocol). *Cochrane Database Syst Rev.* 2013:9;CD010724.[458] Bolignano *et al.* Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev.* 2014;CD007004.[168]
SoF tables	Supplementary Tables S7–S9, S32–S35
Clinical question	**In patients with CKD with chronic hyperkalemia and diabetes, compared to usual care, does the use of potassium binders improve clinically relevant outcomes and reduce clinically relevant harms?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and chronic hyperkalemia and diabetes (T1D and T2D)
Intervention	Potassium binders
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: hyperkalemia, AKI
Study design	RCT
Cochrane systematic reviews	Natale *et al.* Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. *Cochrane Database Syst Rev.* 2020;6:CD013165.[461]
SoF tables	Supplementary Tables S42–S46
Clinical question	**Do antiplatelet therapies improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D and T2D)
Intervention	Antiplatelet therapy

(*Continued on following page*)

Table 2 | (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline chapter 1	Comprehensive care in patients with diabetes and CKD
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S47–S49
Clinical question	**Does smoking cessation versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D and T2D)
Intervention	Smoking-cessation interventions
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S9
Clinical question	**Does bariatric surgery versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D and T2D)
Intervention	Bariatric surgery
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S57
Clinical question	**In patients with diabetes and CKD, do pharmaceutical weight-loss therapies, compared to placebo, no treatment, or standard of care, improve weight-loss or body-weight outcomes?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T1D and T2D)
Intervention	Weight-loss therapies (olistat, phentermine, saxenda, liraglutide, lorcaserin, bupropion-naltrexone, topiramate, acarbose, miglitol, pramlintide, exenatide, zonisamide, fluoxetide, semaglutide, dulaglutide)
Comparator	Placebo/standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S23, S83–S87
Guideline chapter 2	**Glycemic monitoring and targets in patients with diabetes and CKD**
Clinical question	**In adults with diabetes and CKD, compared to HbA1c, do alternative biomarkers improve clinically relevant outcomes and decrease clinically relevant harms?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Alternative biomarkers (glycated albumin, fructosamine, carbamylated albumin)
Comparator	HbA1c or blood glucose monitoring
Outcomes	All-cause mortality, kidney failure, CKD progression—doubling of SCr, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCT, observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S14
Clinical question	**In adults with diabetes and CKD, compared to HbA1c, does blood glucose monitoring (CGM, SMBG) improve clinically relevant outcomes and decrease clinically relevant harms?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Glucose monitoring (CGM, SMBG)
Comparator	HbA1c
Outcomes	All-cause mortality, kidney failure, CKD progression—doubling of SCr, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCT, observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S15, S50

(*Continued on following page*)

Table 2 | (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline chapter 2	Glycemic monitoring and targets in patients with diabetes and CKD
Clinical question	**Does reducing blood glucose to a lower versus higher target improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Tight glycemic control (<7% HbA1c target or fasting glucose levels <120 mg/dl [6.7 mmol/l]), <6.5% HbA1c target, or <6.0% HbA1c target)
Reference standard	Standard glycemic target
Outcomes	Outcomes listed in Table 1
Study design	RCT
Cochrane systematic reviews	Ruospo *et al.* Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Database Syst Rev.* 2017;CD010137.[250]
SoF tables	Supplementary Tables S11–S13
Guideline chapter 3	**Lifestyle interventions in patients with CKD and diabetes**
Clinical question	**Does exercise/physical activity versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Exercise/physical activity (aerobic training, resistance training)
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	Heiwe and Jacobson. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev.* 2011;CD003236.[325]
SoF tables	Supplementary Tables S21, S22
Clinical question	**Do dietary interventions versus usual diet improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Low-salt diets, low-potassium diets, low-phosphate diets, low-protein diets, dietary patterns (caloric-restriction diet, whole-food diets, Mediterranean diet, DASH diet, vegetarian diet)
Comparator	Usual diets
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	McMahon *et al.* Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev.* 2015:2;CD010070.[460] Palmer *et al.* Dietary interventions for adults with chronic kidney disease. *Cochrane Database Syst Rev.* 2017;4:CD011998.[462]
SoF tables	Supplementary Tables S16–S20 and S52–S56
Guideline chapter 4	**Glucose-lowering therapies in patients with T2D and CKD**
Clinical question	**In patients with T2D and CKD, what are the effects of glucose-lowering medication on clinically relevant outcomes and clinically relevant harms?**
Population	Adults with CKD (G1–G5, G5D, G1T–G5T) and diabetes (T2D)
Intervention	Older therapies—metformin, sulfonylureas, or thiazolidinediones More recent therapies—alpha-glucosidase inhibitors, GLP-1 RA, DPP-4 inhibitors
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes for GLP-1 RA: BMI, body weight Long-term harms: amputation, bone fractures, hypoglycemia, lactic acidosis
Study design	RCT
Cochrane systematic reviews	Lo *et al.* Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev.* 2018;9:CD011798.[129] Lo *et al.* Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev.* 2017;2:CD009966.[459]
SoF tables	Supplementary Tables S23 and S60–S91
Guideline chapter 5	**Approaches to management of patients with diabetes and CKD**
Clinical question	**What are the most effective education or self-management education programs to improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Education and self-management programs
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: fatigue and quality of life
Study design	RCT

(*Continued on following page*)

Table 2 | (Continued) **Clinical questions and systematic review topics in the PICOM format**

Guideline chapter 5	Approaches to management of patients with diabetes and CKD
Cochrane systematic reviews	Li *et al.* Education programmes for people with diabetic kidney disease. *Cochrane Database Syst Rev.* 2011;6:CD007374.[408]
SoF tables	Tables S24–S25, S92, S93
Clinical question	**What are the most effective healthcare delivery programs to improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?**
Population	Adults with CKD (G1–G5, G5D) and diabetes (T1D and T2D)
Intervention	Health service delivery programs/models of care
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: fatigue and quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S26–S28 and S94

ACEi, angiotensin-converting enzyme inhibitor(s); AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BMI, body mass index; CGM, continuous glucose monitoring; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; G, glomerular filtration rate category (suffix D denotes dialysis and suffix T denotes transplant recipient); G1T, CKD G1 after transplantation; G5D, CKD G5 treated by dialysis; G5T, CKD G5 after transplantation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; PICOM, Population, Intervention, Comparator, Outcome, Methods; RAS, renin–angiotensin system; RCT, randomized controlled trial; SCr, serum creatinine; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SMBG, self-monitoring of blood glucose; SoF, Summary of findings; T1D, type 1 diabetes; T2D, type 2 diabetes.

studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of the Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including clinicaltrials.gov, and the International Clinical Trials Register search portal.

For review topics that matched existing Cochrane Kidney and Transplant systematic reviews, an updated search of the Cochrane Kidney and Transplant Registry of studies was conducted. The Cochrane Kidney and Transplant Registry of studies was also searched for RCTs not associated with existing Cochrane systematic review. The search strategies are provided in Appendix A: Supplementary Table S1.

The titles and abstracts resulting from the searches were screened by a member of the ERT and confirmed independently by another member of the ERT; if necessary, the full text was assessed, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

The 2020 guideline search identified 5667 citations. The updated 2022 search identified 1078 citations that were screened. Of these, 102 RCTs were included in the updated evidence review. In total, 346 RCTs, 31 observational studies, and 50 systematic reviews have been included in the evidence review (Figure 36).

Data extraction. Data extraction was performed independently by a member of the ERT and confirmed by a second member of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner were included. Any differences among members of the ERT regarding how to perform extraction were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. As the guideline update evidence review only included RCTs, the Cochrane Risk of Bias tool[465] was used to assess individual study limitations based on the following items:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias? Including an assessment of the studies sponsors involvement in study design, conduct, and reporting.[466]

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. The evidence synthesis and meta-analysis methods undertaken for the *KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD* guideline were followed for the 2022 guideline update.

Measures of treatment effect. Dichotomous outcome (all-cause mortality, cardiovascular mortality, kidney failure, cardiovascular events [MACE and individual events—myocardial infarction, stroke, heart failure], doubling of serum creatinine, moderately increased albuminuria to severely increased albuminuria progression, hypoglycemia requiring third-party assistance, etc.) results were expressed as RR with 95% CI. For time-to-event data (MACE), HR with 95% CI was reported; when continuous scales of measurement were used to assess

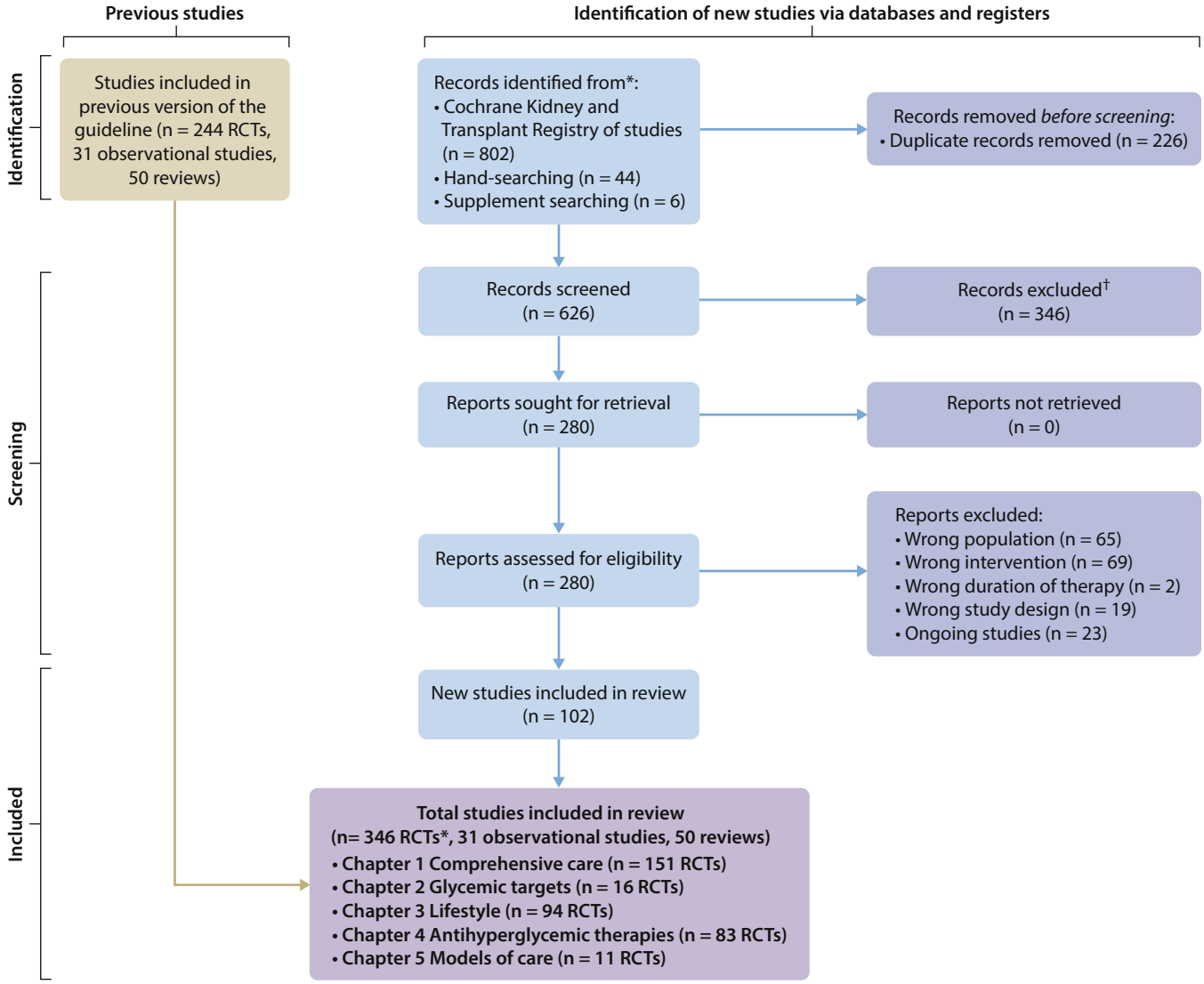


Figure 36 | Search yield and study flow diagram. *A number of randomized controlled trials (RCTs) overlap across chapters in the guidelines. †Screening for RCTs only.

the effects of treatment, such as HbA1c, etc., the mean difference (MD) with 95% CI was used.

Data synthesis. Data were pooled using the Mantel–Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[463] The generic inverse variance random-effects analysis was used for time-to-event data.

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and χ^2 tests. A $P < 0.05$ was used to denote statistical heterogeneity, with an I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[463] We used conventions of interpretation as defined by Higgins *et al.*, 2003.[467]

Assessment of publication bias. We made every attempt to minimize publication bias by including unpublished studies (e.g., by searching online trial registries and conference abstracts). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., more than 10 studies).[463] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity. Subgroup analysis was undertaken to explore whether clinical differences between the studies may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming, rather than hypothesis-testing, and should be interpreted with caution. The following subgroups were considered: type of diabetes, severity of CKD, dialysis modality, age group (pediatric or older adults), and type of intervention—for example, short-acting versus long-acting GLP-1 RA. The test

Table 3 | Classification for certainty and quality of the evidence

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 will be far from the true effect.

of subgroup differences used the I^2 statistic and a P value of 0.1 (noting that this is a weak test).[463]

For glucose-lowering therapies, subgroup analysis was undertaken to assess effect modification of the population of the included studies. Studies that were designed specifically to assess the effects of glucose-lowering therapy in people with CKD and T2D (e.g., CREDENCE) were compared to studies in people with T2D that reported subgroups of people with CKD (e.g., DECLARE TIMI 58) to assess any subgroup differences.

Sensitivity analyses. The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted

Grading the quality of the evidence and the strength of a guideline recommendation. *Grading the quality of the evidence for each outcome across studies.* The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach,[135,464] which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. The quality 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,[135] low event rates in either arm, CIs 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.[135] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Tables 3 and 4).

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population and the intervention and comparator. In addition, the SoF tables include results from the data synthesis as relative and absolute effect estimates. The grading of the quality of the evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in the Data Supplement Appendix C and Appendix D published alongside the guideline or at https://kdigo.org/guidelines/diabetes-ckd/org.

Updating and developing the recommendations. The guideline statements from the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD[155] were considered in the context of new evidence by the Work Group Co-Chairs and Work Group members, and updated as appropriate. Recommendations were revised during virtual meetings in 2021–2022 and by e-mail communication. The final draft was sent for external public review, and reviewers provided feedback for consideration by the Work Group.

Table 4 | GRADE system for grading quality of evidence

Study design	Starting grade of the quality of the evidence	Step 2—lower the grade	Step 3—raise the grade for observational studies
RCT	High	Study limitations: −1, serious −2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious Publication bias: −1, serious −2, very serious	

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial.

Table 5 | KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	Clinicians	Policy
Level 1, strong "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, weak "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.

KDIGO, Kidney Disease: Improving Global Outcomes.

Based on feedback, the guideline was further revised by the Work Group, as appropriate. All Work Group members provided input on initial and final drafts of the guideline statements and guideline text, and approved the final version of the guideline. The ERT also provided a descriptive summary of the evidence quality in support of the graded recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as strong or weak (Table 5). 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 quality of the evidence, patient values and preferences, resource use and costs, and other considerations (Table 6).

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

The overall quality of evidence. The overall quality of the evidence was based on the quality of evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded A, B, C, or D (Table 3).

Patient preferences and values. The Work Group included 2 people living with diabetes and CKD. These members' unique perspectives and lived experience, in addition to the Work Group's understanding of patient preferences and priorities, also 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.

Resource use and costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.[468] 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 clinicians 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 for which a larger quality of evidence was identified. These were developed when no formal systematic evidence review was undertaken, or if there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they may be based on limited evidence. Practice points are sometimes formatted as a table, a figure, or an algorithm, to make them easier to use in clinical practice.

Table 6 | Determinants of the strength of recommendation

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 provided.
Quality of evidence	The higher the quality of the evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the 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, when possible, or were assessed in the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the cost of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1; weak, level 2) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by key information (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. In most cases, an underlying rationale supported each practice point.

Limitations of the guideline development process

The evidence review for the guideline update prioritized RCTs as the primary source of evidence, and study types beyond RCTs have not been considered for the update. However, considering the short timeframe between the previous guideline version (2020)[155] and the guideline update (2022), there is unlikely to be practice-changing evidence beyond RCTs. The search strategy for the guideline update has relied on a well-maintained, expertly controlled database of RCTs in kidney disease. However, the search strategies were not exhaustive, as specialty and regional databases were not searched, and hand-searching of journals was not performed for the included reviews. 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.

Biographic and disclosure information

Ian H. de Boer, MD, MS (Work Group Co-Chair), is professor of medicine and adjunct professor of epidemiology at the University of Washington in Seattle, WA, USA. Dr. de Boer received his medical degree from Oregon Health Sciences University. He trained in internal medicine at the University of California, San Francisco, and in nephrology at the University of Washington, where he also earned a master's degree in epidemiology. Dr. de Boer practices nephrology at the Puget Sound Veterans Affairs Healthcare System and is the director of the Kidney Research Institute at the University of Washington.

Dr. de Boer's research focuses on the prevention, diagnosis, and treatment of diabetic kidney disease and its complications. His epidemiology work has helped define the clinical course of kidney disease in types 1 and 2 diabetes, including prevalence, incidence, risk factors, outcomes, relationships with cardiovascular disease, and the impact of diabetes treatments; his additional work also employs patient-oriented physiology research and clinical trials. Dr. de Boer has published more than 350 manuscripts in the field and was elected to the American Society for Clinical Investigation for these research contributions. He served on the American Diabetes Association (ADA) Professional Practice Committee from 2016 to 2019, chairing the complications subgroup, which oversaw development of the Standards of Medical Care in Diabetes, and is currently deputy editor of the *Clinical Journal of the American Society of Nephrology*.

IHdB reports consultancy fees from AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Cyclerion Therapeutics, George Clinical, Goldfinch Bio, Eli Lilly and Company, Medscape, and Otsuka/Ironwood; and grant support from Dexcom, JDRF*, and Novo Nordisk*.*
**Monies paid to institution.*

Peter Rossing, MD, DMSc (Work Group Co-Chair), is a clinician researcher devoted to the study of complications in diabetes with a focus on renal and cardiovascular complications. He obtained a specialist degree in internal medicine and endocrinology in 2004. Since 2007, he has been a chief physician and manager of the Steno Diabetes Center research team dedicated to the research of microvascular and macrovascular complications of diabetes.

As a professor in diabetic angiopathy at the University of Copenhagen, Denmark, since 2012, Dr. Rossing has conducted epidemiologic studies investigating key features of the pathophysiology of the diabetic kidney at different stages. He has identified several markers for the development of diabetic nephropathy, making it possible to predict individual risk. Dr. Rossing has been involved in several intervention studies in patients with overt diabetic nephropathy, aimed at improving the prognosis.

He is the coordinator of the EU FP7 project PRIORITY, demonstrating that urinary proteomics can be used to stratify the prevention of renal complications in type 2 diabetes, and the Novo Nordisk Foundation grant PROTON, aimed at personalizing prevention of diabetic nephropathy.

He received the Minkowski prize in 2005, the Golgi prize in 2016 (both from the European Association for the Study of Diabetes [EASD]), and the E. Bierman award from the ADA. Dr. Rossing has also served as president of the Danish Endocrine Society and the European Diabetic Nephropathy Study group, and as chairman of the Danish National Diabetes Registry.

PR reports consultancy fees from Astellas, AstraZeneca*, Bayer Pharmaceuticals*, Boehringer Ingelheim*, Gilead*, and Novo Nordisk*; grant support from AstraZeneca* and Novo Nordisk*; speaker fees from AstraZeneca*, Boehringer Ingelheim*, Eli Lilly and Company*, and Novo Nordisk*; educational presentations for Merck*; and stock/stock options from Novo Nordisk.*
**Monies paid to institution.*

M. Luiza Caramori, MD, PhD, MSc, is an associate professor at the University of Minnesota, Minneapolis, MN, USA. Dr. Caramori received her medical degree in Brazil (1990) and did her fellowships in endocrinology and diabetes in Brazil and the US. After receiving her Master of Sciences degree (1997), Dr. Caramori completed her research training in diabetic kidney disease at the University of Minnesota (1998–2002), initially sponsored by the Brazilian government and later by the Juvenile Diabetes Research Foundation (JDRF).

Dr. Caramori's clinical passion lies in providing outstanding care to patients with diabetes. She has served as the director of the Joint Commission Accredited Inpatient Diabetes Service at the University of Minnesota Medical Center since 2016. Dr. Caramori's main interests include studies on the relationships

between kidney structure and function, early molecular and structural predictors of diabetic kidney disease, and clinical trials studying repurposed and new drugs for the prevention and treatment of diabetic kidney disease. Dr. Caramori has authored more than 50 publications in peer-reviewed journals, and 18 book chapters. She has been funded by grants from the National Institutes of Health (NIH), JDRF, and the National Kidney Foundation (NKF) of Minnesota, among others. Currently, Dr. Caramori is the principal investigator of an NIH R01 grant to study protective factors in diabetic kidney disease.

Dr. Caramori was a member of the NKF Kidney Disease Outcomes Quality Initiative (KDOQI) Work Group and helped to develop the 2007 Clinical Practice Guidelines and Recommendations for Diabetes and CKD. Dr. Caramori is the past-chair of the diabetic nephropathy subcommittee for the ADA Scientific Sessions (2018–2020). She also volunteers her time to aid important initiatives of the JDRF, ADA, and American Society of Nephrology (ASN).

MLC reports consultancy fees from AstraZeneca, Bayer Pharmaceuticals, and Boehringer Ingelheim; grant support from Bayer Pharmaceuticals, Boehringer Ingelheim*, and Novartis; and speaker fees from Bayer Pharmaceuticals.*
**Monies paid to institution.*

Juliana C.N. Chan, MBChB, MD, FHKCP, FHKAM, FRCP, is chair professor of medicine and therapeutics and a director at the Hong Kong Institute of Diabetes and Obesity at the Chinese University of Hong Kong. She is a physician scientist specializing in diabetes and clinical pharmacology. In 1995, she developed a data-driven integrated-care model to establish the Hong Kong Diabetes Register (HKDR) for individualizing care and monitoring outcomes, while the accompanying biobanks were used for genetic discovery in pursuit of precision medicine.

In 2000, this research-driven quality improvement program formed the template for a territory-wide risk assessment and management program, which contributed to a 50% to 70% decline in the death rate in people with diabetes in Hong Kong from 2000 to 2016, while creating a population-based diabetes database for knowledge discovery. In 2007, she designed the Joint Asia Diabetes Evaluation (JADE) Technology, which enables systematic data collection for risk stratification and personalized reporting with decision support to promote collaborative research in Asia.

Professor Chan has published over 500 peer-reviewed articles and 20 book chapters. She is a member of steering committees of international projects and outcome trials. In 2019, Professor Chan received the ADA Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes. In 2020, in collaboration with global experts, she led the Lancet Commission on Diabetes to advocate using data to transform diabetes care and patient lives.

JCNC reports board membership with Asia Diabetes Foundation; consultancy fess from AstraZeneca, Bayer Pharmaceuticals*, Boehringer Ingelheim*, Celltrion, Merck Sharp & Dohme*, Novartis*, Roche*, Sanofi*, and Viatris*; grant support from Applied Therapeutics*, AstraZeneca*, Eli Lilly and Company*, Hua Medicine*, Lee Powder*, Merck*, Pfizer*, and Servier*; speaker fees from AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim*, Merck*, Merck Sharp & Dohme*, Sanofi*, Viatris*; educational presentations for Boehringer Ingelheim*; being founding director and shareholder of startup biogenetic testing company GEMVCARE, with partial support by the Hong Kong government; and being co-inventor for the patent of biomarkers for predicting diabetes and its complications.*
**Monies paid to institution.*

Hiddo J.L. Heerspink, PhD, PharmD, is professor of clinical trials and personalized medicine and a clinical trialist at the Department of Clinical Pharmacy and Pharmacology at the University Medical Center Groningen, The Netherlands. He is also a visiting professor at the University of New South Wales in Sydney, Australia. He studied pharmacy at the University of Groningen and subsequently received his PhD from the University Medical Center Groningen. He worked as a postdoctoral fellow at The George Institute for Global Health, Sydney, Australia, where he investigated the effects of blood pressure–lowering regimens on renal and cardiovascular outcomes in patients with CKD.

Professor Lambers-Heerspink's research interests focus on optimizing current treatment strategies and finding new therapeutic approaches to halt the progression of kidney and cardiovascular diseases in patients with diabetes, with a specific focus on personalized medicine. He leads and participates in clinical trials focused on kidney and cardiovascular complications of type 2 diabetes. His main expertise includes clinical trial design and personalized medicine, as well as methodological aspects and statistical analyses of clinical trials.

Professor Lambers-Heerspink has received grants from the Netherlands Organisation of Scientific Research, the Young Investigator Research Award from the European Foundation for the Study of Diabetes, the Harry Keen Award from the EASD, and several personal grants to develop novel strategies to improve the treatment for patients with type 2 diabetes and kidney complications. He is an editorial board member of the *Clinical Journal of the American Society of Nephrology* and served as guest editor for scientific journals including *Diabetes Obesity & Metabolism* and *Nephrology Dialysis Transplantation*. He has authored and coauthored over 350 peer-reviewed publications.

HJLH reports consultancy fees from Abbvie, AstraZeneca*, Bayer Pharmaceuticals*, Boehringer Ingelheim*, Chinook*, CSL Behring*, Dimerix, Gilead*, Goldfinch Bio, Janssen*, Merck & Co*, Mitsubishi Tanabe*, Mundipharma,*

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**Monies paid to institution.*

Clint Hurst, BS, is a retired special education teacher now living in Boerne, TX, USA. Clint received a bachelor's degree from Wayland Baptist University in Plainview, TX, USA, in 1988. Clint worked for many years in the Permian Basin as a Completion Engineer until his health failed, and then he became a special education teacher for seventh and eighth graders. Clint served in the US Army during the Vietnam War. Clint is married, has 3 sons and 10 grandchildren, and is active in his church. He received a kidney transplant on June 13, 2017, at the Michael E. DeBakey VA Medical Center in Houston, TX, USA.

CH declared no competing interests.

Kamlesh Khunti, MD, PhD, FRCP, FRCGP, FMedSci, is professor of primary care diabetes and vascular medicine at the University of Leicester, UK. He is also director of the UK National Institute for Health Research (NIHR) in Applied Research Collaborations (ARC) East Midlands, director of the Centre for Ethnic Health Research, and director of The Real World Evidence Unit. He has led a work program during the Covid-19 pandemic and is a member of the UK Government's Scientific Advisory Group for Emergencies (SAGE) and chair of the SAGE Ethnicity Subpanel. He has published over 1100 peer-reviewed articles. He is also Honorary Visiting Professorial Fellow with Department of General Practice, University of Melbourne. He has won numerous awards nationally and internationally.

KK reports consultancy fees from Amgen, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi, and Servier; speaker fees from Amgen, AstraZeneca, Bayer Pharmaceuticals, Berlin-Chemie AG/Menarini Group, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Napp, Novartis, Novo Nordisk, Roche, and Sanofi; grant support from AstraZeneca, Boehringer Ingelheim*, Eli Lilly and Company*, Janssen*, Merck Sharp & Dohme*, Novartis*, Novo Nordisk*, Roche*, and Sanofi*; and general support from National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM), and NIHR Leicester Biomedical Research Centre (BRC).*
**Monies paid to institution.*

Adrian Liew, MBBS, MRCP(UK), FAMS, FRCP(Edin), FASN, MClinEpid, is a senior consultant nephrologist and director of The Kidney & Transplant Practice at Mount Elizabeth Novena Hospital in Singapore. He received his medical degree from the National University of Singapore and is an elected Executive and Honorary Secretary of the International Society for Peritoneal Dialysis (ISPD). He was the immediate past elected member of the Executive Committee and Council of the International Society of Nephrology (ISN), and the immediate past Chair of the ISN Oceania-Southeast Asia Regional Board. He currently chairs the ISN End-Stage Kidney Failure Strategy Dialysis Subgroup and the ISN Renal Disaster Preparedness Working Group. He is a member of the ISN Dialysis Working Group, the ISN Continuing Medical Education (CME) Committee, and the Asia-Pacific Society of Nephrology (APSN) CME Committee. He received the John Maher Award from the ISPD in 2020 for his contribution to the field of peritoneal dialysis research.

Dr. Liew is associate editor for the journal *Nephrology* and serves on the editorial board for *Kidney International, Peritoneal Dialysis International, Kidney and Blood Pressure Research*, and *Kidney Research and Clinical Practice*. He is a Scientific Leader with George Clinical and his research interests include glomerular diseases, peritoneal dialysis, and diabetic kidney disease. He sits on the steering committees and is the national leader for several multicenter clinical trials.

AL reports consultancy fees from Alnylam Pharmaceuticals, AstraZeneca, Baxter Healthcare, Bayer Pharmaceuticals, Boehringer Ingelheim, Chinook Therapeutics, DaVita Inc, Eledon, George Clinical, Otsuka Pharmaceuticals, and Pro-Kidney; and speaker fees from Baxter Healthcare, Chinook Therapeutics, DKSH Singapore, and Otsuka Pharmaceuticals.

Erin D. Michos, MD, MHS, FAHA, FACC, FASE, FASPC, is an associate professor of medicine in the division of cardiology at Johns Hopkins University, Baltimore, MD, USA, with a joint appointment in the Department of Epidemiology at the Bloomberg School of Public Health. She is the director of women's cardiovascular health and associate director of preventive cardiology with the Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease.

Dr. Michos is an internationally known expert in preventive cardiology and has authored over 550 publications and 10 book chapters. Her research has focused on: (i) cardiovascular disease among women, (ii) coronary artery calcium and inflammatory markers, (iii) lipids, and (iv) diabetes and cardiometabolic disease.

She is co-Editor-in-Chief for the *American Journal of Preventive Cardiology*, an associate editor for *Circulation,* a member of the Board of Directors for the American Society of Preventive Cardiology (ASPC), and a member of the American College of Cardiology (ACC) Prevention Leadership Council. She is also a member of ACC's Clinical Quality Approval Committee (CPAC). Dr. Michos has also held several leadership positions within the American Heart Association (AHA) including being a member of the AHA Funding Committee.

Dr. Michos is a co-investigator in the National Institutes of Health–funded Multi-Ethnic Study of Atherosclerosis (MESA) and Atherosclerosis Risk in Communities (ARIC) cohorts. She is the training director for 3 American Heart Association Strategic Focused Research Networks. She has mentored over 60 individuals in her career and was the recipient of 2 mentoring awards at Johns Hopkins University.

Dr. Michos completed medical school at Northwestern University and then completed both an internal medicine residency and cardiology fellowship at the Johns Hopkins Hospital. She also completed her Master of Health Science degree in cardiovascular epidemiology at the Johns Hopkins Bloomberg School of Public Health.

EDM reports consultancy fees from AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Esperion, Novartis, Novo Nordisk, and Pfizer.

Sankar D. Navaneethan, MD, MS, MPH, is a professor of medicine (tenured), associate chief and director of clinical research at the section of nephrology, and associate director of the Institute of Clinical and Translational Research at Baylor College of Medicine, Houston, TX, USA. He earned his medical degree from Madras Medical College, India, his MPH degree (epidemiology) from the University of South Carolina, and a Master of Science degree in clinical research from Case Western Reserve University, Cleveland, OH, USA. He completed his residency, chief residency, and clinical nephrology fellowship at the University of Rochester, Rochester, NY, USA in 2008. He is a clinician scientist with major research interests in clinical trials in diabetic kidney disease, obesity, and intentional weight loss in CKD, cardiovascular disease in kidney disease, health services research, and systematic reviews in nephrology.

He has authored over 275 peer-reviewed publications and is currently involved in multiple clinical studies and has received independent funding from both the NIH and the Veterans Administration. He has served as associate editor for the *American Journal of Kidney Diseases* since 2017, section editor for *Current Opinion in Nephrology and Hypertension*, associate editor of *CardioRenal Medicine*, and has been appointed to editorial boards of other leading nephrology journals. He also served as a co-editor of the Nephrology Self-Assessment Program (NephSAP-CKD), a premier publication of the ASN from 2015 to 2019. He also serves on various committees of the NKF and the ASN.

SDN reports consultancy fees from AstraZeneca, ACI Clinical, Bayer Pharmaceuticals, Boehringer Ingelheim/Lilly, Vertex, and Vifor.

Wasiu A. Olowu, MBBS, FMCPaed, graduated from the College of Medicine of the University of Lagos, Nigeria in 1985. He trained in postgraduate pediatric medicine and nephrology at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Osun State, Nigeria, between 1988 and 1993. He has been the chair of the Pediatric Nephrology and Hypertension Unit, Department of Pediatrics, OAUTHC, since 1994.

Dr. Olowu has been a full professor of pediatric nephrology at the Department of Pediatrics and Child Health, Obafemi Awolowo University, Nigeria, since 2009, and is currently the chair of the department.

He is clinically focused on AKI, CKD, and follow-up with nephrotic and hypertensive patients. His research interests include the pathologic basis for AKI of secondary origin and the clinicopathologic correlation between proteinuric nephropathy and AKI.

He is a co-investigator on the role of *APOL1*, *MYH9*, and other risk variants and susceptibility to CKD in sub-Saharan African children and adults as part of an H3AFRICA kidney disease research network initiative.

Dr. Olowu has more than 50 journal publications, primarily in nephrology. He is currently associate editor of the *Nigerian Journal of Health Sciences*. Dr. Olowu was an international member of the Abstract Review Sub-Committee at the *World Congress of Nephrology* in Vancouver, Canada, in 2011. He has been a member of the editorial board of the *World Journal of Nephrology* since 2011. Dr. Olowu has reviewed for *Pediatric Nephrology* and *Kidney International*, among other nephrology journals.

WAO declared no competing interests.

Tami Sadusky, MBA, received a pancreas and kidney transplant in 1993 and a second kidney transplant in 2011. She was diagnosed with type 1 diabetes at the age of 13, and within 20 years, she had developed complications from the disease, including kidney failure. The transplants brought her a new life.

Tami received her BS and MBA degrees prior to moving to Washington, where she worked at the University of Washington (UW), Seattle, WA, USA for 22 years as Executive Director of Research Finance and Operations. She is now an active volunteer in the areas of organ donation and transplantation and has been invited to speak about both her pre- and post-transplant patient experience. She is on the board of directors for Transplant House, a nonprofit organization that provides housing for transplant patients. She is an active member of the UW Transplant Advisory Council, the UW Kidney Education and Support Group, the UW Team Transplant Strategic Planning and Finance Committee, and the Kidney Research Institute Advisory Council, and she works closely with the Northwest Kidney Centers. In 2020, Tami established a UW endowment, the Sadusky Endowed Fund for Diabetes, Kidney, and Transplant Research, which supports diabetes, kidney, and transplant research.

Tami has been involved with KDIGO for the past 2 years, helping to develop the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD in addition to the 2022 Guideline Update.

TS declared no competing interests.

Nikhil Tandon, MBBS, MD, PhD, is professor of endocrinology at the All India Institute of Medical Sciences, New Delhi, India. He is a clinician–researcher specializing in diabetes and endocrine care, with a key interest in chronic disease epidemiology and intervention studies to address cardiometabolic risk. He has participated in the leadership of several implementation research studies, funded through the National Institutes of Health and Wellcome Trust, including the mPower Heart Study, the CARRS Translation Trial, the SimCard study, the INDEPENDENT trial, mWELLCARE, and I-TREC (a T4 Translation Trial implementing noncommunicable disease care across an entire block within a district).

He is a technical advisor for the National Programme for the Prevention and Control of Cancer, Diabetes, CVD, and Stroke, and leads the Technical Coordinating Unit for the Youth Onset Diabetes Registry supported by the Indian Council of Medical Research.

He has authored more than 550 peer-reviewed publications in international and national journals, which have been cited more than 56,000 times. He is a fellow of the National Academy of Medical Sciences, the Indian Academy of Sciences, and the National Academy of Sciences (India), and has been conferred the Padma Shri, the Government of India's fourth-highest civilian award. He has served on the Board of Governors of the Medical Council of India and is presently on the Governing Board (as vice president) of the National Board of Examinations.

NT reports grant support from Government of India; Indian Council of Medical Research; National Heart, Lung, and Blood Institute/National Institutes of Health; and Novo Nordisk.

Katherine R. Tuttle, MD, FASN, FACP, FNKF, is the executive director for research at Providence Health Care, co-principal investigator of the Institute of Translational Health Sciences, and professor of medicine at the University of Washington, Spokane, WA, USA. Dr. Tuttle earned her medical degree and completed her residency in internal medicine at Northwestern University School of Medicine, Chicago, IL, USA. She was a fellow in metabolism and endocrinology at Washington University, St. Louis, MO, USA. Her nephrology fellowship training was performed at the University of Texas Health Science Center, San Antonio, TX, USA.

Dr. Tuttle's major research interests are in clinical and translational science for diabetes and CKD. She has published over 300 original research contributions and served 2 terms as Associate Editor for the *Clinical Journal of the American Society of Nephrology* and the *American Journal of Kidney Disease*. Dr. Tuttle has received many honors and awards, including the Medal of Excellence from the American Association of Kidney Patients, the Garabed Eknoyan Award from the NKF, the YWCA Woman of Achievement Award in Science, and 2 Outstanding Clinical Faculty Awards at the University of Washington. Dr. Tuttle is chair of the Diabetic Kidney Disease Collaborative Task Force for the ASN and served on the inaugural Board of Directors for the Kidney Health Initiative. She has chaired numerous kidney and diabetes-related working groups and committees for organizations including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)/NIH, the NKF, the ASN, the ISN, and the ADA.

KRT reports consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Gilead, Goldfinch Bio, Novo Nordisk, and Travere; grant support from Bayer Pharmaceuticals, Goldfinch Bio*, Novo Nordisk*, and Travere; and speaker fees from AstraZeneca, Eli Lilly and Company, Gilead, Goldfinch Bio, Janssen, and Novo Nordisk.*
**Monies paid to institution.*

Christoph Wanner, MD, is professor of medicine and head of the Division of Nephrology at the University Hospital of Würzburg, Würzburg, Germany. Professor Wanner is recognized for his contributions to the field of cardiovascular disease, lipid disorders, and statin treatment in hemodialysis patients

with diabetes. Following the publication of the 4D study in 2005, his research interest moved to earlier stages of diabetes mellitus–induced vascular and kidney damage. Recently, he was acknowledged for his work with the sodium-glucose cotransporter-2 inhibitor empagliflozin impacting cardiovascular and kidney disease outcomes.

Dr. Wanner has published more than 850 scientific papers and articles on rare and common kidney diseases, most of them in major journals. Dr. Wanner was previously a member of the KDIGO Executive Committee and chair of the European Renal Association (ERA) Registry. He has received the Outstanding Clinical Contributions to Nephrology Award from the ERA in 2016, and the Franz Volhard Medaille from the German Society of Nephrology in 2018. He was awarded a doctor *honoris causa* from the Charles University, Prague, Czech Republic, in 2012. Dr. Wanner is President of the ERA for the June 2020–2024 term.

CW reports being a board member for Bayer Pharmaceuticals, Boehringer Ingelheim, Genzyme-Sanofi, Gilead, GlaxoSmithKline, Idorsia, Merck Sharp & Dohme, and Tricida; receiving consultancy fees from Akebia, Amicus, Chiesi, and Vifor Fresenius Medical Care Renal Pharma; and speaker fees from Amgen, Amicus, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Eli Lilly and Company, Fresenius Medical Care, Genzyme-Sanofi, Merck Sharp & Dohme, Novartis, and Takeda.

Katy G. Wilkens, MS, RD, believes the primary role of the renal dietitian is to teach. Whether it is writing, speaking at events, educating peers and students, demonstrating healthy cooking techniques on television, developing patient education materials, or sitting down with one of her hemodialysis patients, Katy finds it rewarding to offer information that can lead others to a healthier future.

The recently retired Nutrition and Fitness Services manager of Northwest Kidney Centers, Seattle, WA, USA, where she oversaw the care of over 2000 dialysis and CKD patients, Katy worked in renal nutrition for 45 years. In addition to helping her patients navigate their dialysis and CKD diets, she mentored dozens of dietetic students in rotations at Northwest Kidney Centers each year and educated fellow healthcare professionals such as physicians, renal fellows, nurses, and social workers.

Katy founded the Washington State Council on Renal Nutrition and the Northwest Renal Dietitians Conference, helping renal dietitians across the 5-state Northwest region connect and network. She is heavily involved in community outreach, speaking at numerous community health events and nutrition and renal conferences, and discussing healthy nutrition regularly on the radio and television.

Katy is the author of the renal chapter in the internationally recognized *Food, Nutrition and Diet Therapy* textbook and the original American Dietetic Association's *Suggested Guidelines for the Care of Renal Patients*. Ms. Wilkens is the editor and author of a nutrition workbook for patients, *Nutrition, the Art of Good Eating for People on Dialysis*. She writes regular nutrition columns for a variety of newspapers, including *Westside Weekly*, *Ballard News-Tribune*, *AgeWise King County*, King County's Senior Services newsletter, NKF newsletters, and others.

Ms. Wilkens has been awarded the Clyde Shields Award for Distinguished Service, in honor of the first dialysis patient in the world. She is a recipient of the Susan Knapp Excellence in Education Award from the NKF in 2013, which is awarded to a renal dietitian who has demonstrated exceptional contributions to renal nutrition education. In 2019, Katy was awarded the Joel Kopple Award by the NKF in appreciation of outstanding service and dedication to renal nutrition. Her two most cherished awards are the Pillar Award given by her peers at Northwest Renal Dietitians for outstanding lifelong commitment to nephrology and the 2021 American Association of Kidney Patients (AAKP) Medal of Excellence award. This award is given based on nomination by kidney patients, and she is humbled by her patients' recognition.

KGW declared no competing interests.

Sophia Zoungas, MBBS, FRACP, PhD, is the head of Monash University's School of Public Health and Preventive Medicine, Melbourne, Victoria, Australia, and also leads the school's Metabolism, Ageing and Genomics Division. She is an endocrinologist with clinical appointments at both Alfred Health and Monash Health, Melbourne, Victoria, Australia. She leads clinical and health services research groups and collaborates extensively both locally and internationally in the specialty areas of diabetes, cardiovascular disease, kidney disease, and healthy aging. She served as president of the Australian Diabetes Society from 2016 to 2018 and clinical director of the National Association of Diabetes Centres from 2009 to 2019. Sophia has over 250 publications in peer-reviewed journals, including the *New England Journal of Medicine*, *Lancet*, *Annals of Internal Medicine*, *British Medical Journal*, and *Nature Reviews*.

SZ reports being an advisory board member for AstraZeneca, Boehringer Ingelheim*, Merck Sharp & Dohme Australia*, Novo Nordisk*, and Sanofi*; speaker fees from Servier Laboratories Australia*; and being an expert committee member for Eli Lilly and Company*.*

**Monies paid to institution.*

KDIGO Chairs

Michel Jadoul, MD, received his MD degree in 1983 at the Université Catholique de Louvain (UCLouvain), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He further spent a year in Utrecht, The Netherlands under Professor Dorhout Mees and Professor Koomans. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc since 2003 and is currently a full clinical professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include β2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has coauthored over 330 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the International Distinguished Medal from the US NKF. He was previously a member of the European Renal Association (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

MJ reports consultancy fees for Astellas, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Fresenius Medical Care Asia Pacific, Mundipharma, and Vifor Fresenius Medical Care; grant support from Amgen, and AstraZeneca*; and speaker fees from Astellas, AstraZeneca, Mundipharma, and Vifor Fresenius Medical Care.*

**Monies paid to institution.*

Wolfgang C. Winkelmayer, MD, MPH, ScD, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medicine, Houston, TX, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Austria, and later earned a Master of Public Health in healthcare management (1999) and a Doctor of Science in health policy (2001) from Harvard University, Cambridge, MA, USA. He then spent 8 years on the faculty of Brigham and Women's Hospital and Harvard Medical School, where he established himself as a prolific investigator and leader in the discipline of comparative-effectiveness research as it pertains to patients with kidney disease. From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, CA, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, TX, USA. Dr. Winkelmayer has authored over 350 peer-reviewed publications, and he has a particular interest in medical publishing. He currently serves as associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He joined KDIGO volunteer leadership as an executive committee member in 2015 and has served as its Co-Chair since 2016.

WCW reports consultancy fees from Akebia/Otsuka, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim/Lilly, GlaxoSmithKline, Merck, Pharmacosmos, Reata, and Zydus.

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Dr. Tonelli's research focuses on improving the care of people with chronic kidney disease and other noncommunicable diseases. He completed a volunteership at the World Health Organization in 2013–2014, focusing on treatment of noncommunicable diseases following natural disasters and civil conflict.

Dr. Tonelli is chair emeritus of the Canadian Task Force on Preventive Health Care, a past President of the Canadian Society of Nephrology, and the former lead of the ISN's global research portfolio. He is a member of and sits on the Executive Committee of the Governing Council for the Canadian Institutes of Health Research.

Dr. Tonelli was the recipient of the 2013 US NKF Medal for Distinguished Service and the Kidney Foundation of Canada's 2013 Medal for Research Excellence for changing nephrology practice in Canada and beyond. He is the Director of the World Health Organization's Collaborating Centre for the Prevention and Control of Chronic Kidney Disease.

Dr. Tonelli has been named a "Highly Cited" researcher each year since 2015 by Thomson-Reuters Web of Science, corresponding to a rank in the top 0.1% by citations of all researchers worldwide.

MAT reports speaker fees from AstraZeneca.

Evidence Review Team

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He has led the formation of state, national, and international networks to conduct high-quality, relevant trials in children. He has been instrumental in the development and implementation of best-practice methods and guidelines relating to CKD in Australia and globally. Professor Craig's many current advisory roles include member of the National Health and Medical Research Council's (NHMRC) Health Translation Advisory Committee, the Pharmaceutical Benefits Advisory Committee, the Medical Services Advisory Committee, and the Commonwealth Department of Health Life Savings Drug Program.

He is a past member of the World Health Organization expert review panel for Global strategy and plan of action on public health, innovation and intellectual property, a past chairman of the Steering Group of the Cochrane Collaboration, and a past member of the Expert Advisory Group for the Structural Review of NHMRC's Grant Program.

JCC declared no competing interests.

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GFMS declared no competing interests.

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As part of Cochrane Kidney and Transplant, David has served as the evidence review project manager for the KDIGO 2022 Clinical Practice Guideline for Diabetes in Chronic Kidney Disease update. David provided methodological expertise on evidence synthesis and guideline development. His role was vital in coordinating the formation of key clinical questions to guide literature searching and leading the data extraction, critical appraisal, meta-analysis, and evidence grading.

DJT declared no competing interests.

Gail Y. Higgins, BA, Grad Ed, Grad Dip LibSc, Information Specialist, completed a bachelor's degree in arts, a graduate diploma in education from the University of Sydney, Sydney, New South Wales, Australia, and a graduate diploma in Library Science from Kuring-gai College of Advanced Education, Sydney, New South Wales, Australia. Following a number of years as a teacher–librarian, she changed tack and spent 3 years with the New South Wales Technical and Further Education (TAFE) Information Systems Division. After that, she joined the University of Sydney Library and worked as a pharmacy librarian and then as an internet training librarian. She has worked as an information specialist for the Cochrane Haematological Malignancies Group in Cologne, Germany, and the Cochrane Cancer Network in Oxford, UK. In 2007 and 2008, she completed a secondment with the World Health Organization in Geneva, Switzerland, on the International Clinical Trials Registry Platform (ICTRP) project.

GYH declared no competing interests.

Patrizia Natale, PhD, MSc (Clin-Epi), Research Associate, is an adjunct lecturer at the University of Sydney (Australia), a research fellow at the University of Bari (Italy), and senior lecturer at University of Foggia (Italy). She has extensive experience in design and conduct of epidemiological studies and evidence syntheses. She has designed and conducted multiple Cochrane systematic

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PN declared no competing interests.

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TEC declared no competing interests.

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NSW declared no competing interests.

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