KDIGO CLINICAL PRACTICE GUIDELINE ON DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE

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PUBLIC REVIEW DRAFT

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

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

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

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

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

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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

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

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

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

Note: Conventional unit x conversion factor = SI unit

ALBUMINURIA CATEGORIES IN CKD

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

ACR, albumin:creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease
*Relative to young adult level
**Including nephrotic syndrome (albumin excretion usually > 2200 mg/24 hours [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-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%)−2.15] × 10.929
Abbreviations: DCCT, Diabetes Control and Complications Trial; 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
ARB	Angiotensin II-receptor blocker
CGM	Continuous glucose monitoring
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial
DPP-4	Dipeptidyl peptidase 4
EASL	European Association for the Study of the Liver
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESKD	End-stage kidney disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1 RA	Glucagon-like peptide-1 receptor agonist(s)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Hemoglobin A1c
HR	Hazard ratio
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major adverse cardiovascular events
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
p.o.	Oral
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RR	Relative risk
SCr	Serum creatinine
SGLT2i	Sodium-glucose co-transporter 2 inhibitor(s)
SMBG	Self-monitoring of blood glucose
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study Group
UK	United Kingdom
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 October 2018 supplemented with additional evidence through September 2019. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health-care 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.

Note: This draft version of the KDIGO Clinical Practice Guideline on Diabetes Management in Chronic Kidney Disease is *not final*. Please do not quote or reproduce any part of this document.

FOREWORD

With the growing awareness that chronic kidney disease (CKD) is a major global 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."

Since 2003, KDIGO has developed a catalog of clinical practice guidelines informing the care of patients with, or at risk of developing, kidney diseases. Currently, KDIGO is updating two existing guidelines on Blood Pressure in CKD and Glomerulonephritis, respectively. In addition, KDIGO has convened a group of experts to develop guideline recommendations related to Diabetes Management in CKD. This is a new guideline area for KDIGO and will be the first to be presented using a new guideline format.

The prevalence of diabetes across the world has reached epidemic proportions. While diabetes is already estimated to affect more than 8% of the global population (more than 350 million people), this is projected to grow to over 550 million people by 2035. More than 40% of people with diabetes will likely develop CKD, including a significant number who will develop end-stage kidney disease (ESKD) requiring dialysis and/or transplantation. With many new agents targeting a variety of mechanistic approaches to improving outcomes for people with diabetes and kidney disease, it appeared timely for KDIGO to commission a guideline in this area.

In keeping with KDIGO's policy for transparency and rigorous public review during the guideline development process, its scope was made available for open commenting prior to the start of the evidence review. The feedback received on the Scope of Work draft was carefully considered by the Work Group members. The guideline draft is now made available for public review, too, and the Work Group will critically review the public input, and revise the guideline as appropriate for the final publication.

We thank Ian de Boer, MD, MS and Peter Rossing, MD, DMSc for leading this important initiative and we are especially grateful to the Work Group members who provided their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from the independent Evidence ReviewTeam (ERT) led by Jonathan Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD; Martin Howell, PhD; and David Tunnicliffe, PhD who made this guideline possible.

KDIGO recently appointed Marcello Tonelli, MD, SM, FRCPC as its first Guideline Methods Chair. He was tasked with improving KDIGO guideline methodology by reinforcing

the linkage between the recommendations and the corresponding evidence, standardizing the guideline format, reducing unnecessary length, and strengthening the utility of the guideline for its users.

To meet these goals, Dr. Tonelli suggested KDIGO work with MAGICapp, a web-based publishing platform for evidence-based guidelines. The program uses a predefined format and allows for direct linkage of the evidence to the recommendation statement. In addition, he introduced a new concept to the format called Practice Points, which were produced in addition to recommendations. Where a systematic review was not done, or was done but did not find sufficient evidence to warrant a recommendation, a Practice Point was used to provide guidance to clinicians. Practice Points do not necessarily follow the same format as recommendations – for example, they may be formatted as tables, figures, or algorithms – and are not graded for strength or evidence quality.

With Dr. Tonelli's guidance and expertise, the use of MAGICapp, and the adoption of Practice Points, KDIGO has seen this guideline on Diabetes Management in CKD develop into a highly useful document, rich in guidance and helpful implementation tools for the user, while still maintaining the high-quality standards and rigor for which KDIGO is best known. The update to the KDIGO guideline format is discussed in greater detail below by Dr. Tonelli.

In summary, we are confident that this GL will prove useful to a myriad of clinicians treating people with diabetes and kidney disease around the world and thanks again all those who contributed to this very important KDIGO activity.

Michel Jadoul, MD
Wolfgang C. Winkelmayer, MD, ScD
KDIGO Co-Chairs

Updates to the KDIGO guideline format

KDIGO guidelines continue to use the GRADE methodology, but we have strengthened the link between evidence and the recommendations themselves.

Guidelines now include a mix of recommendations and "Practice Points" to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice Points are a new addition to KDIGO guidance, and may be formatted as a Table, a Figure, or an Algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and simultaneously posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below is an FAQ outlining the rationale for this shift along with an example recommendation in the new format.

Practice Points are used when	Recommendations will be provided when
• No systematic review was conducted	• Systematic review was conducted
• There is insufficient evidence	• Ample evidence is available
• Evidence was inconclusive (less evidence than required)	• Evidence shows a clear preference for one action over the alternatives
• The alternative option is illogical	• Consensus statements are supported with evidence and explicit discussion of the balance of benefits and harms, values and preferences will be necessary
• The guidance does not imply action for the physician	• Application of guidance requires explicit discussion of values and preferences or on resource
• Consensus statements providing guidance and guidance in the absence of evidence may consider benefits and harms but will not be explicitly discussed	• Guidance is always actionable
• Guidance does not require an explicit discussion of values and preferences or of resource considerations, although is implied that these were considered	• The guidance is more useful displayed as or requires additional explanation in text
• The guidance may be more useful as a table/figure/algorithm	

Information on Guideline Development Process

Who

- A Work Group of experts is convened to develop KDIGO guidelines based on evidence and clinical judgment.
- A designated Evidence Review Team will systematically review and analyze the evidence.
- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is used to analyze certainty in the evidence and strength of guideline recommendations.

How

- Where the Work Group determines that the quality of evidence or strength/importance of the statement warrants a graded recommendation, the text will be organized into structured sections (see below).
- Strength, quality, and magnitude of evidence (published or empirical) will indicate grading of the recommendation.
- Where the Work Group judges that there is a lack of evidence or consensus based clinical practice statements are more appropriate, they may choose to develop a practice point.

What are the structured sections that are included in a recommendation?

Following each Recommendation, there should be a short remark of one to two sentences **summarizing the most important factors** considered when making the Recommendation statement.

Next, the **Key Information** write-up is comprised of five specific subsections representing factors that the Work Group considered both in developing and grading the Recommendation. The sections are:

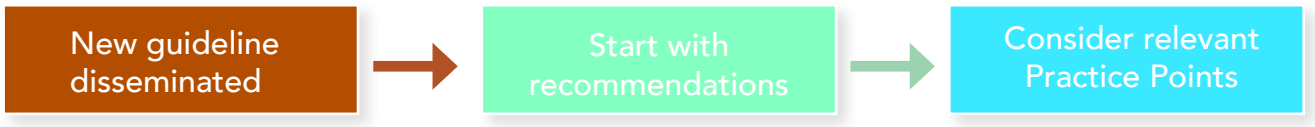
1. Balance of benefits and harms,
2. Quality of evidence,
3. Values and preferences,
4. Resource use and costs, and
5. Considerations for implementation.

The final section of the write-up is a **Rationale** section which serves two purposes. First, the rationale expands on the short remark that immediately follows the Recommendation summarizing how the Work Group considered the five factors of the Key Information section when drafting the recommendation.

Second, the Rationale may be used to describe any key differences between the current KDIGO recommendation and recommendations made in the previous guideline or by other guideline producers.

How should I use Practice Points when caring for my patients?

- As noted, Practice Points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quality of evidence was identified.
- Note that Practice Points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, Practice Points are not graded for strength of recommendation or quality of evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.



What happened to the old “ungraded statements”?

Ungraded statements were often useful to clinicians, but some were not strictly necessary, and their format (i.e., as imperative statements) was not suitable for every situation.

The added flexibility to present Practice Points in alternative formats such as Tables, Figures, and Algorithms should make them more useful to clinicians. Since shorter documents are easier to use, we have tried to eliminate superfluous statements from the guideline and to retain only those that are necessary for providing patient care.

Why did KDIGO make these changes?

The main rationale for the changes was to improve rigour (better link of evidence to recommendations; standardized and consistent format), reduce unnecessary length, and enhance utility to practitioners (clinically useful guidance through Practice Points; visually appealing Tables, Figures and Algorithms that are easier to use at point of care).

Example of new recommendation and practice point format

Treatment

Recommendation 1. We recommend that metformin be used as the first-line treatment for hyperglycemia in patients with T2D who have eGFR ≥ 30 ml/min/1.73m^2 (1B)

Why was this formatted as a recommendation?

- Balance of benefits and harms (all based on published, scientific studies):
  - Benefits: HbA1c reduction, greater weight reduction compared to other drugs, protective against cardiovascular events in general population, etc.
  - Harms: potential for lactic acid accumulation
- The quality of evidence: to form this recommendation was based on clinical recommendations extracted from RCTs, systematic reviews performed in the general population, and outcomes from observational studies were considered.
- Resources and other costs: least expensive, widely available, affordable.
- Considerations for implementation: dose adjustments are required, no safety data for patients with eGFR < 30 ml/min/1.73m2 and must be switched off when this level is reached.

Practice Point 1. Treat kidney transplant recipients with T2D and eGFR ≥ 30 ml/min/1.73m^2 with metformin according to recommendations for patients with T2D and CKD

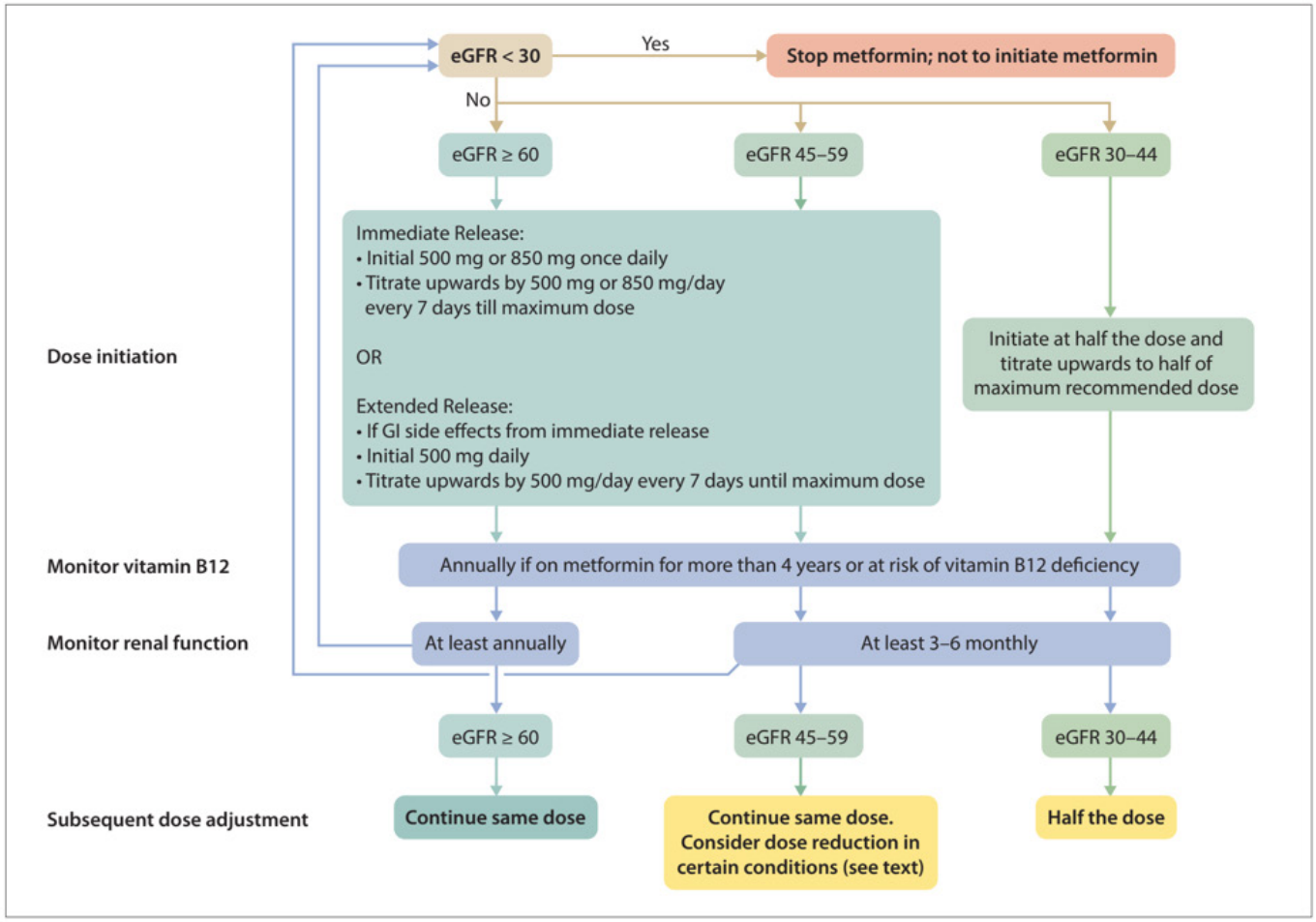
Why was this formatted as a Practice Point?

- Less robust data than recommendation; no systematic review was done.
- Few studies found, most data from registry and pharmacy claims. This evidence cannot be considered conclusive.
- Based on the limited evidence available, the Work Group decided to base their guidance to use metformin in the transplant population should be based on the eGFR, same approach for CKD group.

Practice Points may also have accompanying algorithms to aid in implementation

For example:

Practice Point 2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is <60 mL/min/1.73m²



Why was this formatted as a practice point?

- Limited evidence to support the guidance but monitoring eGFR in these patients is necessary.
- No systematic review was done.
- An Algorithm was a clear visual presentation of the approach to monitoring; one can imagine trying to describe this algorithm in a series of statements, but the graphic is more useful to the reader.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Diabetes Management in Chronic Kidney Disease represents the first KDIGO guideline on the topic. The scope includes topics such as glycemic monitoring and targets, lifestyle and anti-hyperglycemic interventions, and approaches to self-management and optimal models of care. The goal of the guideline is to generate a useful resource for clinicians and patients by providing actionable recommendations with useful infographics based on a rigorous formal literature systematic review. Another aim is to propose research recommendations for areas where there are gaps in knowledge. The guideline targets to a broad audience of clinicians treating diabetes and CKD while being mindful of implications for policy and payment. 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, with areas of future research also presented.

Keywords: chronic kidney disease; glomerular diseases; glycemia; glycemic, HbA1c, metformin, SGLT2 inhibitors, GLP-1 receptor agonists, lifestyle, models of care, dialysis; hemodialysis; KDIGO; guideline; systematic review; evidence-based

INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

This is an opportune time to publish the first KDIGO Clinical Practice Guideline on Diabetes Management in Chronic Kidney Disease (CKD). Worldwide, the estimated number of people with diabetes and CKD has grown in proportion to the rising prevalence of diabetes itself, driven largely by obesity, sedentary lifestyle, an epidemic of Type 2 diabetes, and also by an increasing incidence of Type 1 diabetes. For people with diabetes, CKD is a potentially devastating condition, markedly increasing cardiovascular risk, and potentially leading to kidney failure requiring dialysis or a kidney transplant. However, recent developments suggest new approaches to improve outcomes.

The last 5-10 years have provided new hope for improved prevention and treatment of CKD among people with diabetes. New drugs and technologies provide improved options to control glycemia and prevent CKD and its progression when added to healthy lifestyle and other standard of care management. Patients, health care providers, and health systems are eager to implement these advances in the most effective and evidence-based manner. This requires integration of new therapies with lifestyle management and existing medications using approaches that engage patients and optimize application of health resources. The goal of this guideline is to provide such guidance.

This guideline is designed to apply to a broad population of patients with diabetes and CKD. Types 1 and 2 diabetes are both addressed, with differences in approach to management highlighted where appropriate. Similarly, the Work Group addressed care for patients with all stages 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 creatinine), persistently reduced estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2), or both for greater than 3 months, in accordance to current KDIGO guidelines.

This is an evidence-based guideline that focuses on clinical management questions that can be addressed with high-quality scientific evidence. In collaboration with an Evidence Review Team, the Work Group refined and selected a series of questions that were both clinically pressing and likely to have a sufficient evidence base to make defensible recommendations. 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 are yet insufficiently evaluated for application to clinical care.

Prevention, screening, and diagnosis of CKD are important clinical topics not covered in this guideline. For patients with diabetes, prevention and screening occur mostly in primary care and endocrinology settings. Most primary care and endocrinology societies advocate multifactorial diabetes management with a focus on good glycemic control to prevent microvascular complications, including CKD, as well as yearly screening for CKD with assessment of urine albumin excretion and eGFR. These are practices we support. 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 heterogenous, 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 where appropriate according to albuminuria or eGFR category. We avoid the term "diabetic kidney disease" to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, though this term is entirely appropriate when this limitation is recognized. We also avoid the term "diabetic nephropathy," an outdated term for which currently there is no consensus definition. Prevention, screening, and diagnosis of new-onset diabetes after transplantation are also important topics that were considered 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." Several critical aspects of this comprehensive care, such as blood pressure and lipid management, were addressed in preceding KDIGO guidelines. These topics were not reviewed for the current guideline, and we refer readers to the preceding KDIGO guidelines and their updates. Fortunately, new treatments relevant to people with diabetes and CKD are currently being developed. However, such treatments were not included in this guideline if well-powered randomized trials with clinical outcomes have not yet been reported.

The Work Group aimed to generate a 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 Evidence Review Team. However, practice points were made when evidence was insufficient to make a recommendation but yet clinical guidance was thought to be warranted. In some situations, recommendations could be made for some groups of patients but not for others. For example, evidence for patients treated with dialysis was often weak, leading to fewer recommendations for this population.

As Co-Chairs, we would like to recognize the outstanding efforts of the Work Group, Evidence Review Team, and KDIGO staff. The Work Group was diverse, multinational,

multidisciplinary, experienced, thoughtful, and dedicated. Notably, the Work Group included two members who have diabetes and CKD who contributed actively as peers to keep the guideline relevant and patient-centered. We are indebted to each and every individual who contributed to this process. We hope that the 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

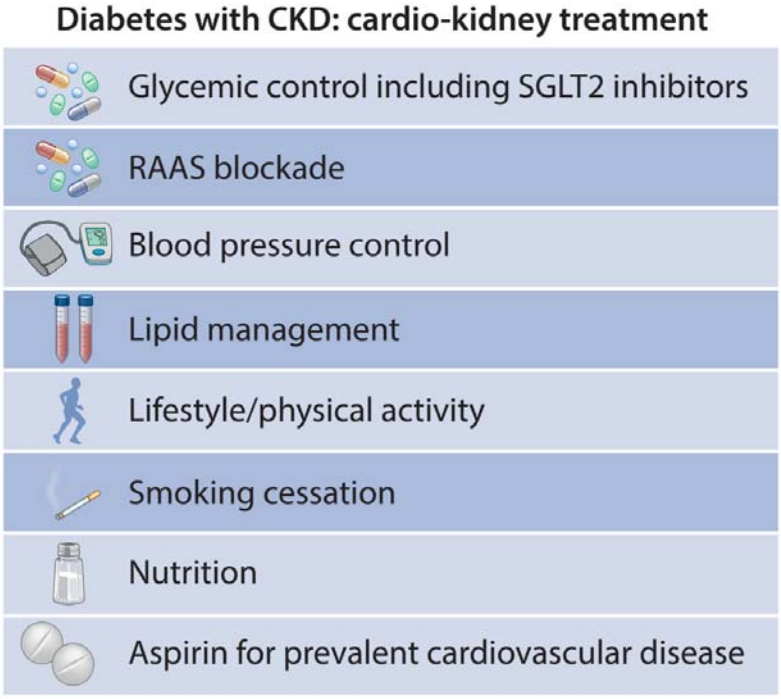
SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

CHAPTER 1. COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

1.1. Comprehensive diabetes and chronic kidney disease management

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

Figure 1. Cardio-kidney risk factor management



1.2. Renin-angiotensin-aldosterone system (RAAS) 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 should be titrated to the highest approved dose that is well tolerated *(1B)*.

Practice Point 1.2.1. Consider ACEi or ARB treatment in patients with diabetes and albuminuria, but have normal blood pressure.

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

Practice Point 1.2.3. Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within four weeks following initiation of treatment or an increase in dose. (Figure 2)

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

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 ACEi or ARB immediately. (Figure 2)

Practice Point 1.2.6. Reduce the dose or discontinue ACEi or ARB in the setting of symptomatic hypotension, uncontrolled hyperkalemia despite medical treatment outlined in Practice Point 1.2.5., or while preparing for imminent kidney replacement therapy.

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

Practice Point 1.2.8. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

1.3. Smoking cessation

Recommendation 1.3.1. We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products *(1D)*.

Practice Point 1.3.1. Physicians should counsel patients with diabetes and CKD to reduce second-hand smoke exposure.

CHAPTER 2. GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD

2.1. Glycemic monitoring

Recommendation 2.1.1. We recommend 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 four times per year if the glycemic target is not met or after change in anti-hyperglycemic therapy.

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

Practice Point 2.1.3. A continuous glucose management indicator (CGMI) 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 self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) may help to prevent hypoglycemia and improve glycemic control when anti-hyperglycemic therapies associated with risk of hypoglycemia are used.

Practice Point 2.1.5. For patients with CKD and Type 2 diabetes who choose not to do daily glycemic monitoring by SMBG or CGM, anti-hyperglycemic agents that pose a lower risk of hypoglycemia are preferred.

Practice Point 2.1.6. CGM devices are rapidly evolving with multiple functionalities (e.g., CGMI, real-time and flash glycemia monitoring). 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 non-dialysis dependent CKD *(1C)*.

Practice Point 2.2.1. Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by SMBG or CGM and by selection of anti-hyperglycemic 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 a 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 protein intake of 0.8 g of protein/kg (weight)/day for those with diabetes and non-dialysis CKD (*2C*).

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

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 corner stone of nutritional management in patients with diabetes and CKD.

Practice Point 3.1.4. Professional nutritionists, registered dietitians, diabetes educators, community health workers, peer counselors or other health workers should be engaged in the nutritional care of patients with diabetes and CKD.

Practice Point 3.1.5. Health care providers should consider cultural differences, intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to the patient and their family.

3.2. Physical activity

Recommendation 3.2.1. We recommend that patients with diabetes and CKD should 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.

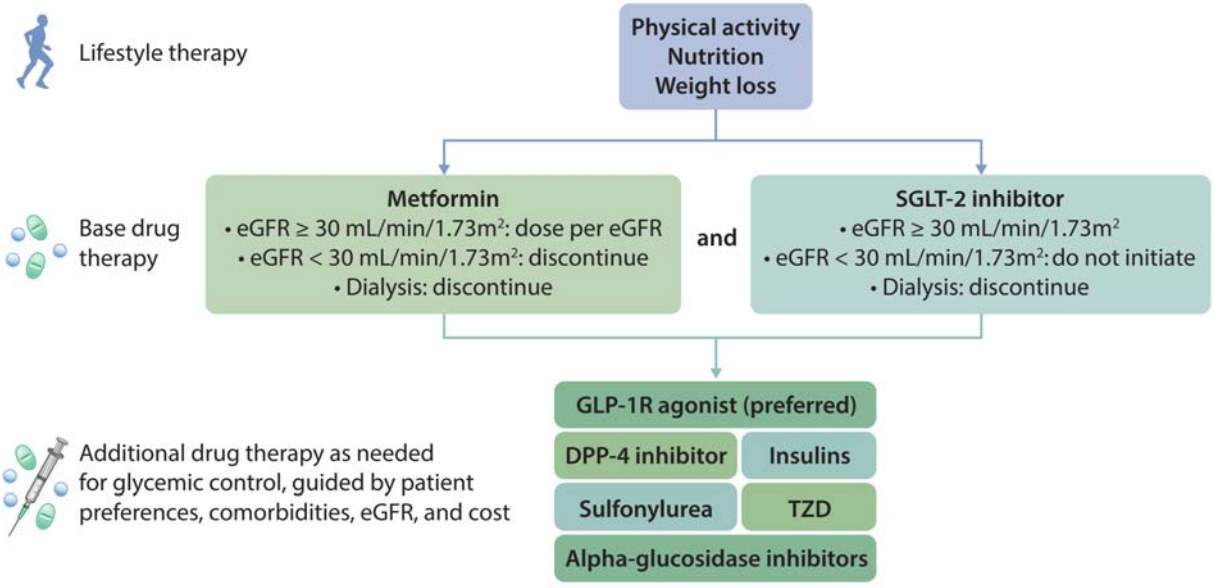
Practice Point 3.2.3. For patients at higher risk of falls, physicians should provide advice on the intensity of physical activity (low, moderate, or vigorous) and type of exercises (aerobic vs. resistance or both).

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/1.73 m^2.

CHAPTER 4. ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Practice Point 4.1. Glycemic management for patients with Type 2 diabetes and CKD should include lifestyle therapy, base drug therapy with metformin and a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, and additional drug therapy as needed for glycemic control (Figure 11).

Figure 11. Glycemic treatment algorithm for patients with T2D and CKD



Practice Point 4.2. Most patients with Type 2 diabetes, CKD, and eGFR ≥30 ml/min/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 (GLP-1) receptor agonists generally preferred.

4.1. Metformin

Recommendation 4.1.1. In patients with Type 2 diabetes, CKD, and eGFR ≥30 ml/min/1.73 m^2, we recommend that metformin be used as the first-line treatment for hyperglycemia *(1B)*.

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

Practice Point 4.1.2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is <60 ml/min/1.73 m^2. (Figure 13)

Practice Point 4.1.3. Adjust the dose of metformin when eGFR is less than 60 ml/min/1.73 m^2. (Figure 13)

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

4.2 Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

Recommendation 4.2.1. In patients with Type 2 diabetes, CKD, and eGFR ≥30 ml/min/1.73 m^2, we recommend including an SGLT-2 inhibitor (SGLT2i) in the antihyperglycemic treatment regimen *(1A)*.

Practice Point 4.2.1. A SGLT2i can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met and for patients who are meeting glycemic targets but can safely attain a lower target. (Figure 14)

Practice Point 4.2.2. For patients in which additional glucose lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.

Practice Point 4.2.3. Choice of SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 4.2.4. It is reasonable to withhold SGLT2i during times of prolonged fasting or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 4.2.5. If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i and advising patients about symptoms of dehydration and low blood pressure, and follow up volume status after drug initiation.

Practice Point 4.2.6. A reversible decrease in eGFR with commencement of SGLT2i may occur and is generally not an indication to discontinue therapy.

Practice Point 4.2.7. Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min/1.73 m^2, unless reversible changes in eGFR are precipitating uremic symptoms or other complications of CKD.

Practice Point 4.2.8. SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients.

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

Recommendation 4.3.1. In patients with Type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin SGLT2i, or who are unable to use those medications, we recommend a long acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) *(1B)*.

Practice Point 4.3.1. The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Practice Point 4.3.2. To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly. (Table 11)

Practice Point 4.3.3. GLP-1 RA should not be used in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors.

Practice Point 4.3.4. The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

CHAPTER 5. APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Section 5.1. Self-management education programs

Recommendation 5.1.1. We recommend a structured self-management educational program be implemented for care of people with diabetes and CKD *(1C)*. (Table 12)

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

Section 5.2. Team-based integrated care

Recommendation 5.2.1. We suggest that policy-makers and institutional decision-makers should 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 non-physician personnel (e.g., nurses, healthcare assistants, community workers, peer supporters). (Figure 19)

CHAPTER 1. COMPREHENSIVE CARE

1.1. Comprehensive diabetes and chronic kidney disease management

Optimal management of chronic kidney disease (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 in center, the team includes medical doctors, nurses, dietitians, educators, lab technicians, chiropodists, family members and potentially many others depending on local organization and structure. In the guideline, the background and organization of this chronic care model is described in Section 5.2 Team Care.

To engage people with diabetes and CKD to self-manage their disease and participate in the necessary shared decision making on the management plan, structured education is critical. Several models have been proposed, as outlined in the dedicated section in the guideline. It is essential that education is structured, monitored, individualized and evaluated in order to be effective.

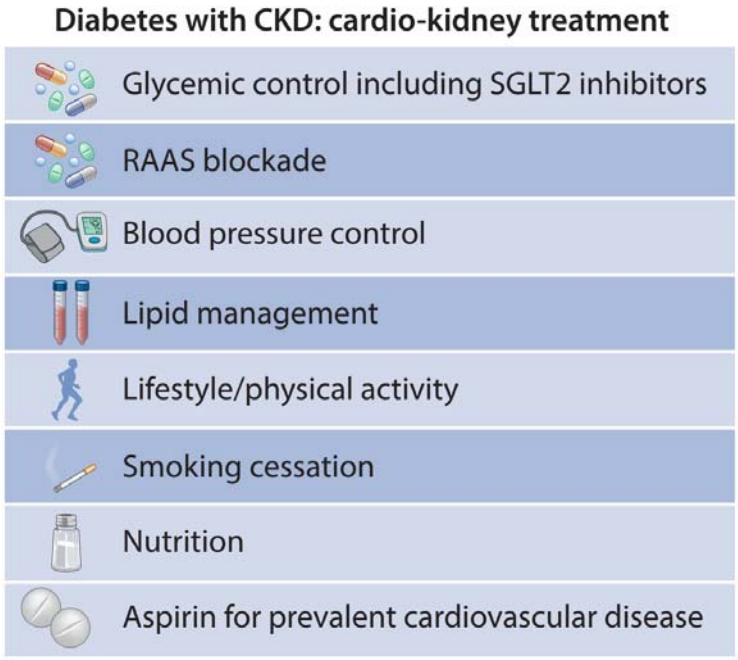
Individuals with diabetes and CKD are at risk for acute diabetes-related complications such as hypoglycemia and diabetic ketoacidosis, long-term complications such as retinopathy, neuropathy and foot complications, and also the risk of end-stage kidney disease (ESKD) with a need for dialysis or transplantation, and in particular the risk of cardiovascular complications, with ischemia, arrhythmia, and heart failure. Management therefore includes regular evaluation for these complications as well as for the many cardiovascular risk factors in addition to hyperglycemia such as hypertension, dyslipidemia, obesity, and lifestyle factors including diet, smoking, and physical activity.

The prognosis in an observational study of Type 2 diabetes (T2D) in Sweden demonstrated how cardiovascular risk and mortality is dependent on the number of uncontrolled risk factors.[1] Multifactorial intervention targeting the risk factors with lifestyle modification including smoking cessation support, dietary counselling, and physical activity, and pharmacological intervention is needed. Studies in people with T2D and early CKD demonstrated the long-term benefit of multifactorial intervention on development of micro- and macrovascular complications and mortality.[2, 3]

The guideline focuses on selected topics where evidence-based guidance can be provided and is not covering topics like blood pressure and lipid management as these topics 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 indicated in Figure 1.

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

Figure 1. Cardio-kidney risk factor management



Abbreviations: CKD = chronic kidney disease, RAAS = renin-angiotensin-aldosterone system (RAAS) blockade, SGLT2 = sodium-glucose cotransporter-2 inhibitors

As kidney function deteriorates and reaches the more advanced CKD stages, management of anemia, bone and mineral disorders, fluid and electrolyte disturbances, and eventually dialysis and transplantation become increasingly dominant in the management. As these topics are also covered by other KDIGO guidelines, 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 and glycemia management as well as lifestyle factors, for all CKD stages.

1.2. Renin-angiotensin-aldosterone system (RAAS) 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 should be titrated to the highest approved dose that is well tolerated *(1B)*.

This recommendation places a high value on the potential benefits of renin-angiotensin-aldosterone system (RAAS) 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.

Key information

Balance of benefits and harms

Moderately or severely elevated albuminuria is related with increased renal and cardiovascular risk compared to normal albumin excretion. The IRMA-2[4] and INNOVATION[5] were placebo-controlled trials enrolling patients with T2D and moderately increased albuminuria (30-300 mg/g or 3-30 mg/mmol). They were designed to determine whether RAAS blockade reduced the risk of progression and CKD in diabetes, defined as the development of severely increased albuminuria (> 300 mg/g or 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 threefold risk reduction with the highest dose (300 mg per day) at two years of follow-up.[4] 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 was placebo after one year of follow-up.[5] 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 RAAS blockade were shown to extend to patients with severely increased albuminuria. Two landmark trials, the IDNT[6] and RENAAL[7] studies, were conducted in patients with T2D and CKD, having albuminuria greater than 1 g/day. 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 non-significant reduction in the incidence of ESKD, which was independent of blood pressure. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, ESKD, or death 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 updated Cochrane systematic review[8] (Table S4[9-39] and Table S5[6, 26, 31, 40-44]) performed by the Evidence Review Team (ERT) concurred that the use of ACEi or ARBs in patients with CKD and diabetes was associated with a reduction in the progression of CKD with regards 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].

ACEi and ARB are generally well-tolerated. The systematic reviews performed suggested that ACEi and ARBs treatment may have little or no difference on 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 one systematic review.[45] It has been postulated to be due to the inhibition of ACE-dependent degradation of bradykinin, and a consideration can be made to switch affected patients to an ARB, where the incidence of angioedema is not significantly different from that of placebo [ARB: 0.11% (95% CI 0.09, 0.13) versus 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 ARBs, but also side effects increase with increasing doses and thus initiation at a low dose and up-titration to the highest approved dose the patient can tolerate. Post hoc analysis of randomized trials and observational cohorts have demonstrated that an initial larger albuminuria reduction is associated with better long-term outcomes.[46, 47]

Quality of the evidence

The overall quality of the evidence was rated as moderate. From randomized control trials (RCTs) that compared ACEi with placebo/standard, the certainty of the evidence for critical outcomes, such as all-cause mortality, moderately increased to severely increased albuminuria progression, and doubling serum creatinine was moderate (Table S4). Additionally, in RCTs that compared ARB with placebo/standard of care, the certainty of the evidence was moderate for these critical outcomes (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 doubling serum creatinine and albuminuria progression and not the cardiovascular outcomes, and adverse events because of the lack of reporting of these outcomes in trials.

Values and preferences

The progression of CKD to ESKD, 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 ARBs 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 RAAS blockade treatment with either an ACEi or ARB for kidney protection effects compared to no treatment. This recommendation applies to both Type 1 diabetes (T1D) and T2D, as well as kidney transplant recipients; however, this does not apply to patients on dialysis.

The evidence does not demonstrate superior efficacy of ACEi over ARB or vice versa, and the choice between these two drug classes will depend on other factors including patient preferences, cost, availability of generic formulations, and side-effects profile of individual drugs. ACEi-induced cough is the predominant cause of intolerance to this class of drug, affecting about 10% of patients.[48] In clinical practice, affected patients are often

switched to an ARB so as not to lose the kidney protective effects of RAAS blockade, though the improvement in tolerability has not been evaluated in a RCT.

Resources and other costs

Generic formulations of both ACEi and ARBs are widely available at low cost in many parts of the world. Moreover, both ACEi and ARBs have been included in World Health Organization (WHO) list of essential medicines.[49]

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 their effect on efferent arteriole dilatation could result in hyperkalemia and a rise in serum creatinine in patients with renal artery stenosis. Consequently, the blood pressure, serum potassium, and serum creatinine should be monitored in patients who are started on RAAS 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 reduced.

Table 1 outlines the common types of ACEi and ARBs available, 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 with different regulatory authorities.

Table 1. Different formulations of ACEi and ARBs

Drug	Starting dose	Maximum daily dose	Kidney impairment
ACE inhibitors			
Benazepril	10 mg once daily	40 mg	Reduce to 25%–50% of usual dose in patients on hemodialysis or peritoneal dialysis. 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/1.73m^2: administer 75% of normal dose every 12–18 hours. CrCl < 10 mL/min/1.73m^2: 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	No dosage adjustment necessary 20% to 50% removed by hemodialysis
Fosinopril	10 mg once daily	80 mg	No dosage adjustment necessary Poorly removed by hemodialysis
Lisinopril	5 mg once daily	40 mg	No dosage adjustment necessary 50% removed by hemodialysis
Perindopril	4 mg once daily	16 mg	Use is not recommended when CrCl < 30 mL/min/1.73m^2 Perindopril and its metabolites are removed by hemodialysis
Quinapril	10 mg once daily	80 mg	No dosage adjustment provided in manufacturer's labelling About 12% of parent compound removed by hemodialysis
Ramipril	2.5 mg once daily	20 mg	Administer 25% of normal dose when CrCl < 40 mL/min/1.73m^2 Minimally removed by hemodialysis
Trandolapril	1 mg once daily	4 mg	Reduce to 50% of usual dose when GFR < 10 mL/min Minimally removed by hemodialysis
Angiotensin receptor blockers			
Azilsartan			
Candesartan	8 mg once daily	32 mg	In patients with CrCl < 30 mL/min/1.73m^2, 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	25 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/1.73m^2, with recommended maximum dose of 20 mg/day. 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/1.73m^2 – to use with caution. Not removed significantly by hemodialysis

Abbreviations: AUC = area under the curve; CrCl = creatinine clearance; GFR = glomerular filtration rate

The use of ACEi and ARBs has been shown to be 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 RAAS 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 development of ESKD in patients with CKD and diabetes. It has also been demonstrated that the degree of albuminuria correlates with the risks for ESKD, and that both ACEi and ARB have been shown to be 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 also side effects as well) and thus starting at a low dose and then up-titration for maximal effect to the highest tolerated and recommended dose. Notwithstanding their anti-albuminuric effects, improvement in kidney outcomes have been demonstrated in multiple RCTs. In addition, both drugs are well-tolerated, and the benefits of treatment outweigh the inconvenience from the need to monitor the kidney function and serum potassium after initiation or change in dose of the drug. This recommendation, therefore, places a high value on the moderate quality evidence demonstrating that RAAS blockade with ACEi or ARBs slows the rate of kidney function loss in patients with CKD and diabetes, and a relatively lower value on the side effects of these drugs and the need to monitor kidney function and serum potassium levels.

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

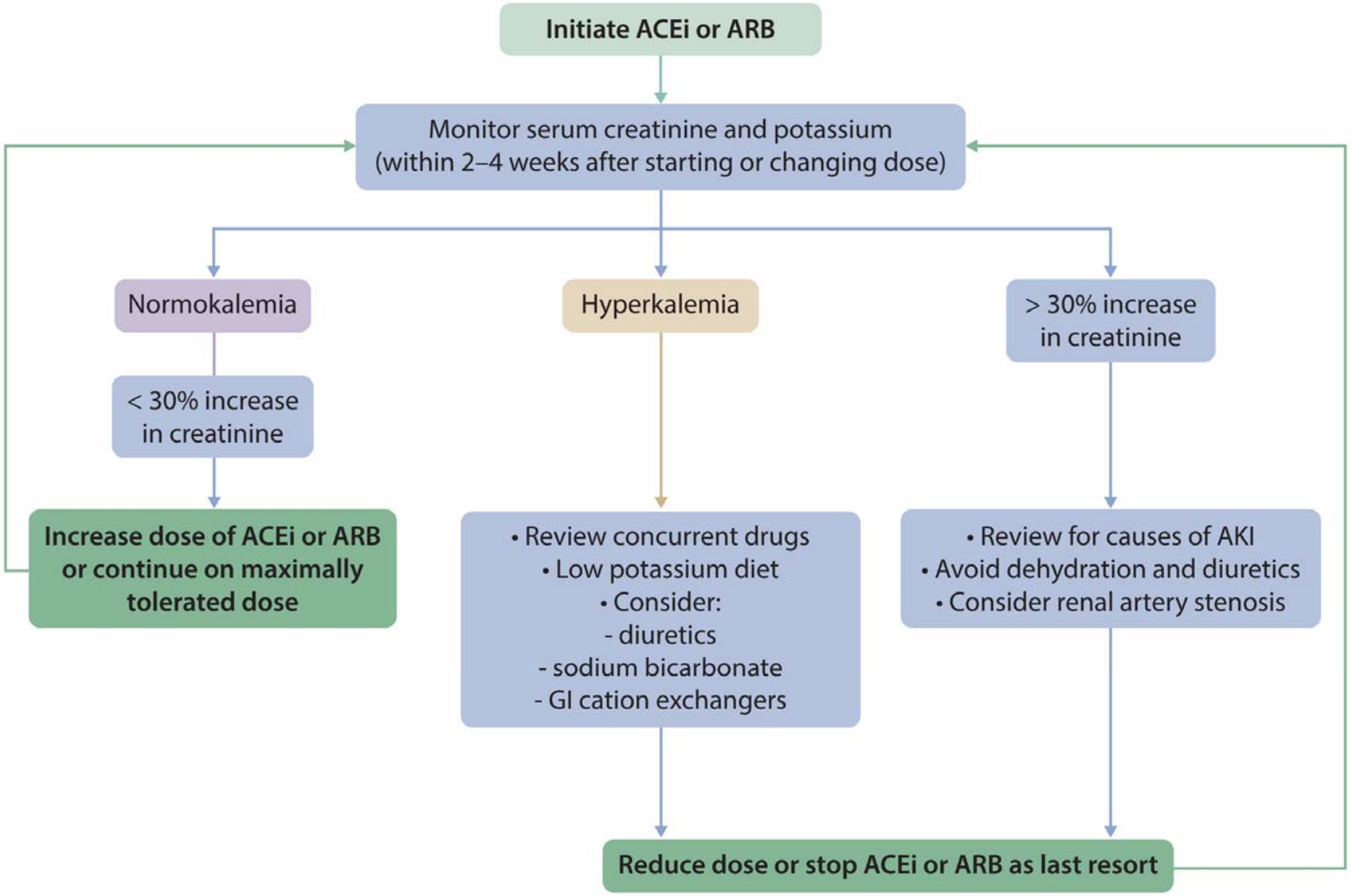
Practice Point 1.2.1. Consider ACEi or ARB treatment in patients with diabetes and albuminuria, but have normal blood pressure.

The benefits of RAAS blockade have been less studied in patients with diabetes and CKD without hypertension. While the IDNT and IRMA-2 study recruited exclusively patients with T2D and hypertension, a small percentage (3.5%) of patients in the RENAAL trial and 163 out of the 527 randomized patients (30.9%) in IRMA-2 were normotensive, suggesting that the use of RAAS blockade may be beneficial in patients without hypertension. Moreover, due to the strong correlation between severity of albuminuria and the risk of ESKD in this population, and given that RAAS blockade reduces the severity of albuminuria, the Work Group judged that ACEi and ARBs may be beneficial in patients with diabetes and albuminuria but without hypertension.

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

ACEi and ARBs are potent anti-hypertensive 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 glomerular filtration rate and a rise in the serum creatinine. In addition, RAAS blockade inhibits the action of aldosterone with a greater propensity for hyperkalemia. An increase in serum creatinine level, if it occurs, will typically happen during the first two weeks of treatment initiation, and should stabilize within two to four weeks in the setting of normal sodium and fluid intake.[50] Therefore, patients should be monitored for symptomatic hypotension, hyperkalemia and excessive rise in serum creatinine within two to four weeks after initiating or change in the dose of the drug, depending on resource availability and patient preferences.

Figure 2. Monitoring of serum creatinine and potassium during ACEi or ARB treatment - Dose adjustment and monitoring of side effects



Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, AKI = acute kidney injury, ARB = angiotensin II receptor blockade, GI = gastrointestinal

Practice Point 1.2.3. Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within four weeks following initiation of treatment or an increase in dose. (Figure 2)

The rise in serum creatinine should not be a deterrent in using ACEi or ARBs in patients with diabetes and CKD, including those with pre-existing kidney insufficiency.[28] Moreover, there was suggestions in clinical trials that the greatest slowing of kidney disease progression occurred in patients with the lowest eGFR at study initiation.[25, 51] A review of 12 RCTs that evaluated kidney disease progression among patients with pre-existing kidney insufficiency demonstrated a strong association between acute increases of serum creatinine of up to 30% from baseline that stabilized within two months of ACEi therapy and long-term preservation of kidney function.[50]

The most common cause of an acute rise in serum creatinine level following the use of a RAAS 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 non-steroidal anti-inflammatory drugs.[52] 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 RAAS blockade treatment, especially in patients with extensive atherosclerotic cardiovascular disease (CVD) or who are smokers.[50] Therefore, in patients with an acute excessive rise in in serum creatinine (>30%), the clinician should evaluate the potentially contributing factors highlighted above 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, and discontinue these agents in women who are considering pregnancy, or who become pregnant while receiving ACEi or ARBs.

The use of drugs that block the RAAS system 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 RAAS blockade agents found that 48% of newborns exposed to ACEi and 87% of those exposed to ARBs developed complications,[53] with long-term outcomes occurring in 50% of the exposed children. Across both exposure to 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.[54, 55] 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.[53]

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 epidemiological evaluation of Medicaid data of 29,507 infants born between 1985 and 2000,[56] which demonstrated that the risks of major congenital malformations, predominantly cardiovascular and neurological abnormalities, were significantly increased among infants exposed to 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.[57] However, the limitation of most of the studies that showed a negative association with first trimester exposure did not account for malformations among miscarriages, pregnancy terminations, and stillbirth. Therefore, the possibility of teratogenesis with first trimester exposure to ACEi and ARBs 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 or ARBs should be avoided. Likewise, women of childbearing age, should be counselled appropriately regarding the risks of ACEi or ARBs exposure during pregnancy and the need for effective contraception. Women who become pregnant while on RAAS blockade treatment should have the drug stopped immediately and 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 ACEi or ARB immediately. (Figure 2)

The cardiovascular and kidney benefits of ACEi and ARBs 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 RAAS blockade and occurs in about 10% of outpatients[58] and up to 38% in hospitalized patients[59] receiving ACEi. Risk factors for the development of hyperkalemia with the use of drugs that inhibit the RAAS system included CKD, diabetes, decompensated congestive heart failure, volume depletion, advanced age, and use of concomitant medications that interfere with kidney potassium excretion.[60] 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.

Therefore, identifying patients at risk of hyperkalemia, and instituting preventive measures should allow these patients to benefit from RAAS blockade. Measures to control high potassium levels include:

a. Follow a low-potassium diet with specific counselling to avoid potassium-containing salt substitute,[61] or food products containing the salt substitute.
b. 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 counselled to discontinue these remedies if present.
c. General measures to avoid constipation including enough fluid intake and exercise.
d. Initiate diuretics treatment to enhance the excretion of potassium in the kidneys.[58]
e. Treatment with oral sodium bicarbonate is an effective strategy in minimizing the risk of hyperkalemia in patients with CKD and metabolic acidosis.[62] Concurrent use with diuretics will reduce the risk of fluid overload that could be a concern from sodium bicarbonate treatment.
f. Treatment with gastrointestinal cation exchangers, such as patiromer or zirconium cyclosilicate, have both been used to treat hyperkalemia associated with RAAS blockade therapy for up to 12 months,[63, 64] and may be considered when the above measures failed to control serum potassium levels. Both studies demonstrated the effectiveness of achieving normokalemia and the ability to continue treatment with RAAS blockade agents, without treatment-related serious adverse effects. However, clinical outcomes were not evaluated, efficacy and safety data beyond one year of treatment is not available, and cost and inaccessibility to the drugs in some countries remain issues with their utilization.

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

Practice Point 1.2.6. Reduce the dose or discontinue ACEi or ARB in the setting of symptomatic hypotension, uncontrolled hyperkalemia despite medical treatment outlined in Practice Point 1.2.5., or while preparing for imminent kidney replacement therapy.

The dose of ACEi or ARBs should only be reduced or discontinued as a last resort in patients with hyperkalemia, after 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 dose of ACEi or ARBs in patients who experience symptomatic hypotension.

When these drugs are used in patients with eGFR <30 ml/min/1.73 m^2, close monitoring of serum potassium is required. Withholding these drugs solely on the basis of the

level of kidney function will unnecessarily deprive many patients of the cardiovascular benefits that they otherwise would have received, 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 temporarily to allow time for kidney replacement therapy preparation.

Practice Point 1.2.7. Use only one agent at a time to block the RAAS. 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 mono therapy with these agents. Long-term outcome trials in patients with diabetes and CKD demonstrated no kidney or cardiovascular benefit of RAAS blockade with combined therapy to block the RAAS versus the single use of RAAS inhibitors. However, combination therapy was associated with a higher rate of hyperkalemia and acute kidney injury[194] and thus only one agent at a time should be used to block the RAAS.

Practice Point 1.2.8. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

The steroidal mineralocorticoid receptor antagonists spironolactone and eplerenone have in small and short-term studies have been found to reduce blood pressure in resistant hypertension[65, 66] (defined as uncontrolled hypertension on three antihypertensive agents including a diuretic) and to lower albuminuria in diabetes patients with elevated urinary albumin excretion.[67] There are no long-term data from RCTs on clinical benefits. In addition, side effects, particularly hyperkalemia and decline in renal function[68], are a concern when added to background therapy with an ACEi or ARB or diuretic, particularly among patients with eGFR <45 ml/min/1.73 m^2.[69] Thus blocking aldosterone may be particularly useful in patients with resistant hypertension without a history of high potassium, and GFR>45, and should not be used with eGFR <45 and high risk of elevated potassium. Whether newer non-steroidal mineralocorticoid receptor antagonists may provide benefit in diabetes and CKD with less side effects is an area of ongoing research.[69]

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 ESKD.
- The effects of mineralocorticoid receptor antagonists on progression of CKD and development of ESKD as well as CVD effects in patients with CKD. Evaluation should also be made on the deleterious effects of supra-maximal doses on hyperkalemia, acute kidney injury and hypotension.

1.3. Smoking cessation

Recommendation 1.3.1. 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 from 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.

Key information

Balance of benefits and harms

Tobacco use remains as a leading cause of death across the globe and is also a known risk factor for the development of CKD.[70] Recent data also highlight the relationship of second-hand smoke with kidney disease.[71] While 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.[72] More recently, Electronic Nicotine Delivery Systems referred to as e-cigarettes have been reported to increase the risk of lung and CVD.[73] 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, health care professionals should assess the use of tobacco products and counsel patients to quit using tobacco products in those with diabetes and CKD.

Quality of evidence

Among people with diabetes and CKD, smoking cessation interventions have only been examined in one small randomized cross-over trial with a total of 25 participants recruited ten of whom did not have diabetes and were not included in the analysis. The timeframe for this study was short term; eight hours of controlled smoking versus eight hours non-smoking (in the same subjects) on separate days. The certainty of the evidence from this study for surrogate outcomes was low because of very serious imprecision (only one study and few participants),

and critical clinical outcomes, such as death, ESKD, and cardiovascular events were not reported and hence the overall quality of the evidence has been rated as very low (Table S6).[74]

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 considered that it would be important to 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 their combination. Behavioral interventions include assessment of tobacco use and willingness to quit followed by counseling during office visit. Clinicians should present available treatment options to those who use tobacco products and make recommendations based on the cost, affordability, and availability. These include Food and Drug Administration (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 health care providers should be considered.

Considerations for implementation

Assessment of tobacco use would help physicians identify high-risk individuals and the benefits of abstinence from tobacco products is not likely to differ based on gender and race. Physicians should consider the affordability (when using nicotine replacement products) and access to various resources while making treatment recommendations. Overall, these recommendations are similar to the 2012 KDIGO CKD guidelines,[201] American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the primary prevention of CVD[75] and the United States (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.[76] Population-based studies note that exposure to second-hand smoke to be associated with a higher prevalence of kidney disease and the development of incident kidney disease. While e-cigarette use has increased over time, their safety, especially with regards to CVD, has been questioned, and their effects on kidney disease are unknown.[77, 78] While 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 higher cardiovascular events among current or prior smokers.[79] 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 non-smokers and former smokers. In the general population, interventions that combine pharmacotherapy and behavioral support increase smoking cessation success.[80] While dedicated trials are lacking in those with CKD, these interventions are likely to confer similar benefits in those with diabetes and CKD.[77]

Practice Point 1.3.1. Physicians should counsel patients with diabetes and CKD to reduce second-hand smoke exposure.

Second-hand smoke exposure increases the risk of adverse cardiovascular events in the general population and their associations with incidence kidney disease have also been reported.[71] As the prevalence of smoking has decreased over time and with restrictions on using tobacco products exposure to second-hand smoke have decreased in certain countries, but the risk persists in several other regions. Thus, while assessing the use of tobacco products, exposure to second-hand smoking should also be assessed, and patients with significant exposure should be advised of the potential health benefits of reducing such exposure.

RESEARCH RECOMMENDATIONS

- The safety, feasibility and beneficial effects of different interventions (e.g., behavioral vs. pharmacotherapy) for quitting tobacco should be further examined in clinical studies.

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CHAPTER 2. GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD

2.1. Glycemic monitoring

Recommendation 2.1.1. We recommend 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 antihyperglycemic treatment. The recommendation places a lower value on inaccuracy of the HbA1c measurement as compared with directly measured blood glucose in advanced CKD.

Key information

Balance of benefits versus harms

HbA1c 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 antihyperglycemic 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).[81-85]

The National Glycated Hemoglobin Standardization Program (NGSP) established a certification process to benchmark calibration of HbA1c measurements.[86] The International Federation of Clinical Chemistry Working Group on HbA1c Standardization developed specific criteria for HbA1c analyses based upon two reference methods, mass spectroscopy and capillary electrophoresis with ultraviolet-visible detection. Despite calibration and standardization, many assays commonly used in clinical settings still have clinically meaningful assay biases (>7% difference from the reference standard at an HbA1c level of 6% (42 mmol/mol) or 9% (75 mmol/mol). HbA1c is also often measured by a point-of-care instrument where standardization remains an issue with the additional limitation of operator variation.

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 in blood. In observational studies, glycated albumin is associated with all-cause and cardiovascular mortality in patients treated by chronic hemodialysis.[87] 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.[88] Fructosamine may also be biased by hypoalbuminemia and other factors.

Two systematic reviews of observational studies in patients with CKD and diabetes found that HbA1c correlated moderately with measures of glucose by fasting or morning blood levels, or mean of continuous glucose monitoring (CGM) particularly among people with eGFR ≥30 ml/min/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 stage 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 four observational studies.[87, 89-91] 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 three glycemic biomarkers, HbA1c, glycated albumin, and fructosamine, were progressively worse with more advanced CKD stages.

Quality of the 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 CKD and diabetes was undertaken, one for the comparison between blood glucose measures and HbA1c and one for the comparison between alternate biomarkers and blood glucose measures. Each review identified 13 studies with three addressing both comparisons (Table S10 and Table S11).[91-100] The overall quality of the studies for this recommendation was difficult to determine due to lack of information provided from the identified studies, but 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 QUADAS-2 tool[101] as there is no agreed upon tool to examine the certainty 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 weak because some patients may choose not to monitor by HbA1c or follow the suggested schedule of testing, especially those with advanced stages of CKD, anemia, or treatment by red blood cell transfusions, erythropoiesis-stimulating agents, or iron supplements.

Resource use and other considerations

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 ESKD 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.

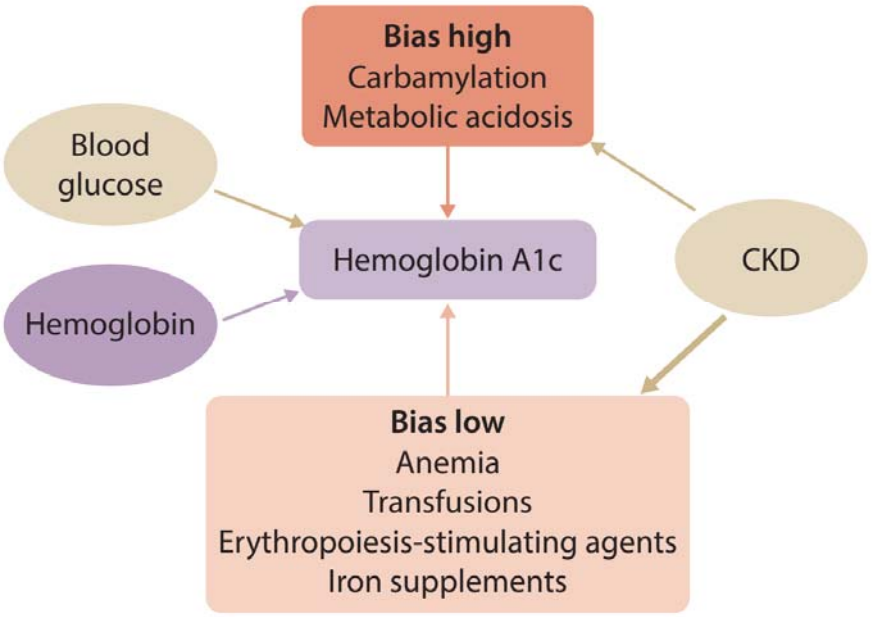
Considerations for implementation

Patients with T1D or T2D and CKD likely benefit from glycemic monitoring by HbA1c. This recommendation is applicable for adults and children of all race/ethnicity and gender groups and to patients with ESKD 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.[102] HbA1c is an advanced glycation end-product of hemoglobin, a principle protein in red blood cells (Figure 3). 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.[103] (Figure 3) HbA1c levels may also be increased in CKD by hemoglobin carbamylation.[104, 105] Conversely, HbA1c is lowered by shortened survival or age of erythrocytes from anemia, transfusions, and use of erythropoiesis-stimulating agents or iron replacement therapies.[103, 106] 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.

Figure 3. Effects of CKD-related factors on advanced glycation end-products and glycemic biomarkers



CKD = chronic kidney disease

HbA1c 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 due to lack of better alternatives. This recommendation applies to patients who have T1D or T2D and CKD with the caveat that reliability of HbA1c for glycemic monitoring is low at more advanced CKD stages (see Table 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 four times per year if the glycemic target is not met or after change in anti-hyperglycemic 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 to 9% (64 to 75 mmol/mol) reduce risk of overall microvascular complications, including nephropathy and retinopathy, and some macrovascular complications in RCTs.[81-85] The potential harm of monitoring by HbA1c is that it may underestimate or overestimate 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 four times per year to align with a 10- to 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 stable patients 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.[107]

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

Correlations of directly measured blood glucose levels with three glycemic biomarkers, HbA1c, glycated albumin, and fructosamine, were progressively worse with advanced CKD stages, especially ESKD treated by dialysis.[87, 88, 94, 99, 108] 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, respectively, with hypoalbuminemia, a common condition among patients with proteinuria, malnutrition, or treated by peritoneal dialysis.

Practice Point 2.1.3. A continuous glucose management indicator (CGMI) 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. Therefore, if it is a clinical concern that HbA1c may be yielding estimates of long-term glycemia that are biased (e.g., discordant with SMBG, random blood glucose levels, or hypoglycemic or hyperglycemic symptoms), it is reasonable to use CGM to generate a continuous glucose management indicator (CGMI), which is a proxy for long-term glycemia in conjunction with the HbA1c measurement in individual patients, allowing adjustment of glycemic goals accordingly.[109, 110] CGMI may commonly 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 CGMI could potentially change over time within patients, particularly when there are changes in clinical characteristics that affect red blood cell turnover or protein glycation. In these situations, CGMI needs to be re-established regularly.

Table 2. Frequency of HbA1c and use of CGMI in CKD

Population	Measure	Frequency of HbA1c	Reliability	CGMI
CKD G1–G3b	Yes	• Twice per year • Up to four 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 four times per year if not achieving target or change in therapy	Low	Commonly useful

CGMI = continuous glucose management indicator, HbA1c = hemoglobin A1c

SMBG and CGM are frequently used but relatively high cost options for daily glycemic monitoring in patients with diabetes. Real-time assessments of glucose promote effective self-management. Risk of hypoglycemia in patients with diabetes treated by many oral agents and insulin is substantially increased by advanced CKD. Daily monitoring improves safety of anti-hyperglycemic therapy by identifying fluctuations in glucose as a means to avoid hypoglycemia. SMBG and CGM also aid in achieving glycemic targets. SMBG was emphasized in previous clinical practice guidelines for daily glycemic monitoring in patients with diabetes and CKD,[110] but 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.

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

In the judgement of the Work Group there is no clear advantage of SMBG or CGM for patients treated by oral anti-hyperglycemic agents.[107] However, in those with CKD and T1D or T2D, daily monitoring may mitigate their higher risk of hypoglycemia associated with taking insulin or certain oral agents (Table 3). 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 SMBG or CGM, especially when anti-hyperglycemic therapies associated with hypoglycemia are used. Anti-hyperglycemic agents not associated with hypoglycemia are preferable therapies for patients with diabetes and CKD who do not use SMBG or CGM, such as those without access to these technologies or ability to do self-monitoring, or preference to avoid the daily burden.

Table 3. Relationship of anti-hyperglycemic drug choice to risk of hypoglycemia and rationale for SMBG or CGM

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

Practice Point 2.1.5. For patients with CKD and Type 2 diabetes who choose not to do daily glycemic monitoring by SMBG or CGM, anti-hyperglycemic 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 anti-hyperglycemic 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 anti-hyperglycemic 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 use of anti-hyperglycemic agents that are not inherently associated with occurrence of hypoglycemia (metformin, SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors).

Practice Point 2.1.6. CGM devices are rapidly evolving with multiple functionalities (e.g., CGMI, real-time and flash glycemia monitoring). 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 the 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 directly communicate with ambulatory insulin pumps and to set alarms for low or high glucose levels, as well as for their rates of raise or decline. These devices differ on 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 ESKD treated by dialysis or kidney transplant, research is needed to:

- Develop methods to identify patients for whom HbA1c has 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 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 non-dialysis dependent CKD *(1C)*.

This recommendation places a higher value on the potential benefits of an individualized target aimed at balancing the 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 where prevention of complications is the key goal, a lower HbA1c target (e.g., <6.5% or <7.0%) might be preferred, while for those with multiple co-morbidities or increased burden of hypoglycemia, a higher HbA1c target (e.g., <7.5% or <8.0%) might be preferred.

Key information

Balance of benefits versus harms

HbA1c targets are central to guide anti-hyperglycemic treatment. In the general diabetes population, higher HbA1c levels have been associated with increased risk of micro- and macrovascular complications. Moreover, in clinical trials, targeting lower HbA1c levels has reduced the rates of chronic diabetes complications in patients with T1D[111-118] or T2D.[119-126] The main harm associated with lower HbA1c targets is hypoglycemia. In the ACCORD trial of T2D, mortality was also higher among participants assigned to the lower HbA1c target, perhaps due to hypoglycemia and related cardiovascular events.[122]

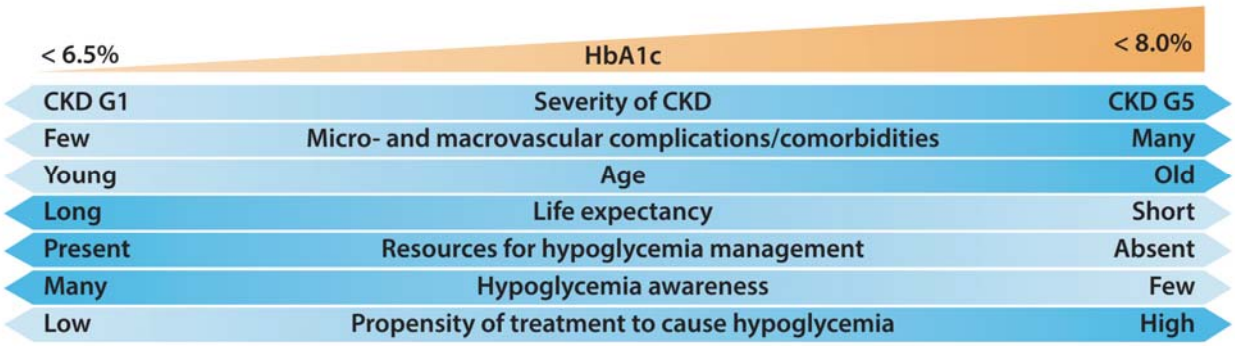
Among patients with diabetes and CKD, a U-shaped association of HbA1c with adverse health outcomes has been observed, suggesting risks with both inadequately controlled blood glucose and to excessively lowered blood glucose.[127] However, the benefits and harms for the proposed HbA1c targets on patients with T2D are derived mostly from studies that used anti-hyperglycemic 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 significant increase in hypoglycemia rates when attained using medications with 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 stages of CKD and ESKD.

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.[83, 128, 129] In addition, and more stringent glycemic control compared with less stringent glycemic control increases risk of hypoglycemia.[122] Individual patient factors modify both anticipated benefits and anticipated risks of more stringent glycemic control (Figure 4). For example, younger patients with few comorbidities, mild-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 trade-offs, while 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.

Figure 4. Factors potentially guiding decisions on individual HbA1c targets



Quality of the evidence

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

The updated Cochrane systematic review[130] identified eleven studies[113, 115, 117, 120, 122, 124-126, 131-133] that compared a target HbA1c <7.0% to higher HbA1c targets (standard glycemic control). Three studies were also identified but could not be included in the meta-analysis.[111, 114, 134] The review found that an HbA1c <7.0% target decreased the incidence of non-fatal myocardial infarction and onset and progression of moderately increased albuminuria, but the certainty 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 ESKD (Tables S7).

Six studies[121, 122, 124-126, 132] compared a target HbA1c of ≤6.5% to higher HbA1c targets (standard glycemic control) found a HbA1c target ≤6.5% probably decreased incidence of moderately increased albuminuria, and ESKD. The certainty of the evidence was rated as moderate for these two outcomes, with downgrading due to study limitations. There was little or no difference or inconclusive data on other outcomes, and the certainty of the evidence was low to very low because of study limitations, heterogeneity, and serious imprecision (Table S8).

Two studies[122, 135] comparing a target HbA1c ≤6.0% to higher HbA1c targets (standard glycemic control) found the lower HbA1c target probably increased all-cause mortality. There was little or no effect on cardiovascular mortality, but the effect estimate is large, and the confidence intervals are close to the null [RR 1.65 (95% CI 0.99, 2.75)]. Similarly, the lower HbA1c ≤6.0% target decreased the incidence of non-fatal myocardial infarction and moderately

increased albuminuria compared to standard glycemic control. The certainty of the evidence was rated as moderate-to-low for these outcomes because of study limitations, and serious imprecision (Table S9).

Overall, the quality of the evidence was graded as low because of study limitations, the inconsistency of results, or imprecision. However, for onset of moderately increased albuminuria, and non-fatal myocardial infarction, the evidence was rated as moderate certainty. Additionally, the majority of the evidence were extrapolated from subgroups of the RCTs in the general population of people with diabetes. However, some studies only included patients with diabetes and moderately increased albuminuria.[117, 125, 121] 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 4). 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, and 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 non-fatal myocardial infarction, and for patients who are able to achieve such targets easily and without hypoglycemia (e.g., patients treated with fewer antihyperglycemic agents and with those 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 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 lower risk of hypoglycemia may be considered 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 co-morbidities. Considerations regarding life-expectancy are also relevant when considering potential beneficial effects of blood glucose-lowering therapy. In patients with T1D, data from RCTs indicate that it may take two to three years for the beneficial effects of a lower HbA1c to be detected, while in patients with T2D this time is estimated at 4.5 years.

Resource use and costs

Lower blood glucose targets may increase costs for monitoring of blood glucose and impose additional burden on the patient. Use of specific glucose-lowering agents (e.g., sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) may have a greater impact in kidney and cardiovascular outcomes in patients with T2D and CKD than reaching specific HbA1c targets.

Considerations for implementation

The proposed HbA1c targets are applicable for all adults and children of all race/ethnicity and sex and to patients with ESKD treated by kidney transplant. The suggested range for HbA1c targets does not apply to patients with ESKD 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, CKD stage, presence of co-morbidities, life-expectancy, hypoglycemia burden, choice of anti-hyperglycemic 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.[122] 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 SMBG or CGM and by selection of anti-hyperglycemic agents that are not associated with hypoglycemia.

Glucose monitoring strategies that may help safe achievement of lower HbA1c targets include use of CGM[136, 137] and SMBG, which are not known to be biased by CKD or its treatments, including dialysis or kidney transplant (see Section 2.1). A CGMI 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. CGMI may commonly be useful for patients with advanced CKD, including those treated with dialysis, for whom 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.

While the accuracy and precision of HbA1c are similar among patients with CKD and eGFR ≥30 ml/min/1.73 m^2 as to the general diabetes population, on average, HbA1c may be inaccurate for an individual patients 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 eGFR <30 ml/min/1.73 m^2. Thus, for some patients, CGM may be used to index HbA1c by demonstrating the association between mean glucose and HbA1c (CGMI), and adjust HbA1c targets accordingly, as noted above. Alternatively, CGM metrics themselves can be used to guide antihyperglycemic therapy. In particular, glucose time in range (70-180 mg/dl) and time in hypoglycemia (<70 mg/dl) have been used as outcomes for clinical trials[138, 139] and have been endorsed as appropriate metrics for clinical care.[140] 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.

RESEARCH RECOMMENDATIONS

- Evaluate the value of CGM and metrics like "time in range" and mean glucose levels as alternatives to HbA1c 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 anti-hyperglycemic agents not associated with increased hypoglycemia risk
- Establish if a lower glycemic target is associated with less progression of established CKD
- Establish optimal glycemic targets in the dialysis population with diabetes.

CHAPTER 3. LIFESTYLE INTERVENTIONS IN PATIENT WITH DIABETES AND CKD

3.1. Nutrition intake

Background

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 they are well aware 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 intakes.

The number of RCTs analyzing the effects of diet among people with diabetes and CKD is small. Most RCTs have 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, multi-center studies and their results needs to be made 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 indicates 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.

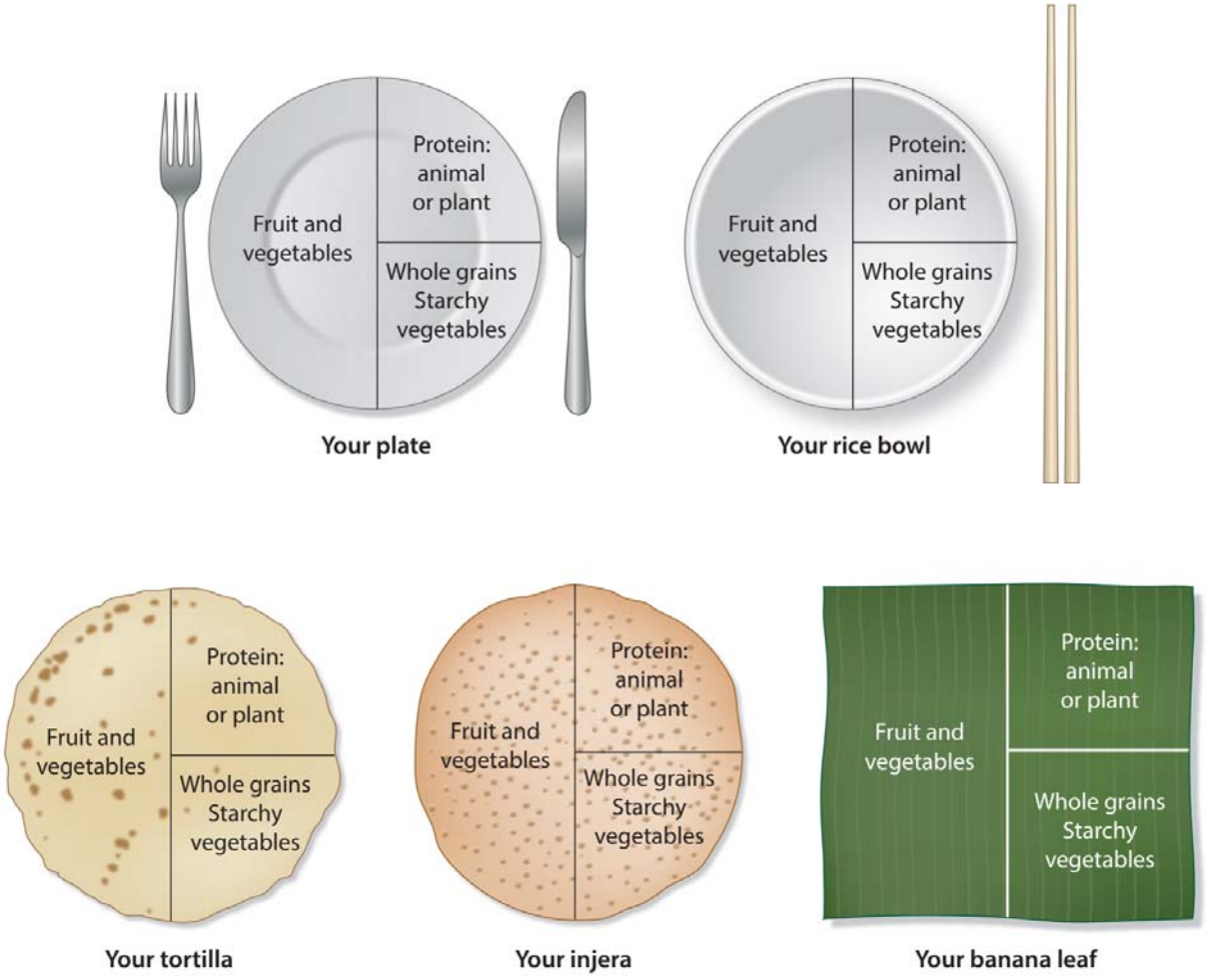
Practice Point 3.1.1. Patients with diabetes and CKD should consume a diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts and lower in processed meats, refined carbohydrates, and sweetened beverages.

People with diabetes and CKD are often asked to follow intricate nutrient intake recommendations, compared with the general population. Indeed, the complexity of combining 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 and is an appropriate starting point for

patients with diabetes and CKD. In the general population, and in the non-diabetic CKD and ESKD population, adherence to healthy eating practices has been shown to offer numerous health benefits.[141] The benefit of consuming less refined and processed foods in the general population is well-established, and hence its applicability to those with diabetes and CKD is also reasonable.

Nutrition therapy can decrease HbA1c levels at levels similar to, or better than, antihyperglycemic medications. Simple advice such as increasing non-starchy vegetables, decreasing added sugars and refined grains and increasing whole foods over highly processed foods can be implemented for most people across wide geographic and economic strata. (Figure 5)

Figure 5. What does a kidney healthy diet look like?



Recommendation 3.1.1. We suggest maintaining protein intake of 0.8 g protein/kg (weight)/day for those with diabetes and non-dialysis CKD *(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.

Key information

Balance of benefits to harms

Compared with a standard dietary protein intake of 0.8 g/kg/day, lower dietary protein intake has been hypothesized to reduce glomerular hyperfiltration and slow progression of CKD.[142] However, limiting protein intake to less than 0.8 g/kg/day in a person with diabetes, who may have also 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 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. 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/day, especially to reduce carbohydrate intake or lose weight. However, long-term effects of high-protein diets (especially >1.0 g/kg/day) on kidney function are not known and could potentially cause harm by requiring increased kidney excretion of amino acids.[143] High protein intake could also increase acid load and precipitate or worsen metabolic acidosis, particularly in those with lower levels of kidney function.

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.[143] A Cochrane systematic review on very low protein diet (0.3 to 0.4 g/kg/d) compared to a low diet (0.5 to 0.6 g/kg/d) or normal protein diet (≥ 0.8 g/kg/d) for 12 months probably had little or no effect on death and or ESKD (moderate certainty of the evidence). The certainty of the evidence was downgraded because of imprecision and inconsistency.[144]

In spite of 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.

An exhaustive 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 (Table S12).[145-155] A systematic review of all study types, including observational studies examining harms caused by high protein diets was conducted, and 1,127 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 CKD and diabetes often have multiple co-morbid 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 moderating 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. Particularly for people facing more progressive CKD and ESKD, they may be highly motivated to implement nutrition solutions to 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.[143] 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 nutritional 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 consider these things may provide the patient with less expensive, healthier meals, contributing to their health and wellbeing, as well as that of their families.

Despite the fact that most people with diabetes do not receive nutritional 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 since 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 3.2.2). Patients with newly diagnosed diabetes should be referred for individualized nutrition education at diagnosis. Patients with long-standing diabetes and CKD should have access to nutrition education yearly as well as at critical times to help build self-management skills.[156]

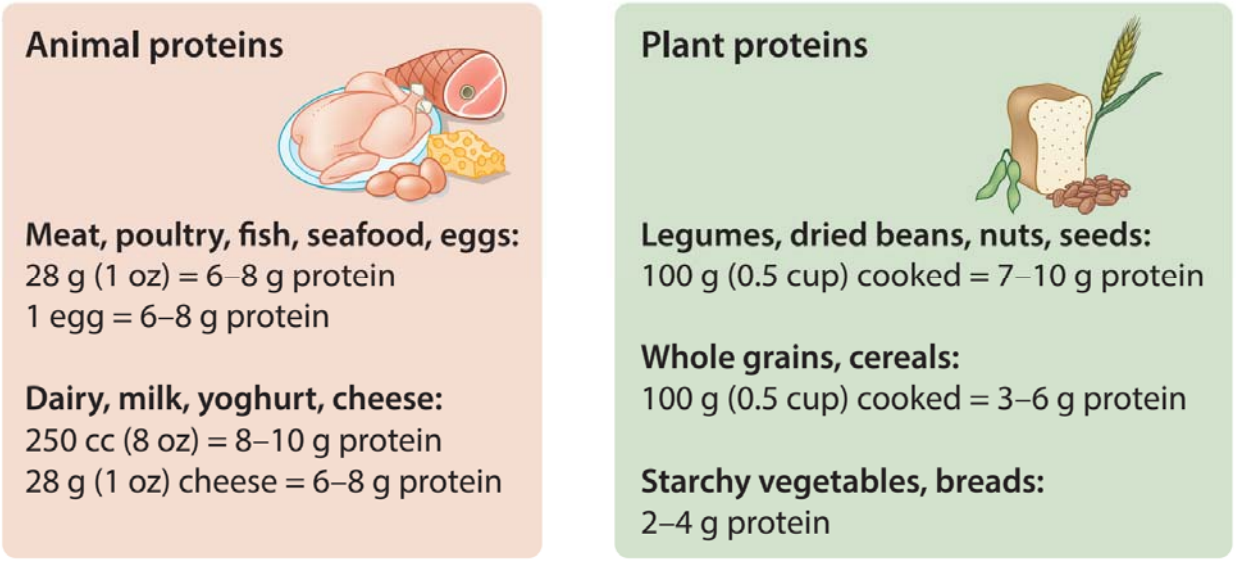
While most patients would be amenable to lifestyle modifications, some may be unwilling or unable to implement these and will need alternative options and substitutions that warrant discussions with them. These include referral peer counseling programs, village health workers, registered dietitians,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

A table of protein guidelines based on 0.8 grams protein/kg for adults with diabetes and CKD not requiring dialysis, is found in Table 4, 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.[143] Alternatively, in overweight patients, clinicians may use an ideal weight to multiply by 0.8 gram protein/kg/day, 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/protein/day with the weight of a food in grams (i.e., 100 grams of meat contains only about 25 grams of protein). (see Figure 6)

Table 4. Protein guideline for adults with diabetes and non-dialysis CKD

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 6. Average protein content of foods in grams



Rationale

High-protein intake contributes to the development of increased intraglomerular pressure and glomerular hyperfiltration which in turn lead to glomerulosclerosis and tubulointerstitial injury.[157] Experimental models and uncontrolled human investigations showed improvement in kidney function with protein restriction. In few clinical studies, predominantly enrolling those with non-diabetic and especially advanced CKD, a low protein intake (compared to those with normal protein intake of 0.8 g/kg/day) has demonstrated to slow down the decline in kidney function.[144] However, clinical trials comparing different levels of protein intake are lacking in those with diabetes and CKD, and thus the Work Group extrapolated data from recommendations of the World Health Organization for protein intake for the general population.[143]

The Work Group also considered the potential harmful impact of very low protein intake (0.4-0.6 g/kg/day) 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.[158] While observational studies have reported that high consumption of red and processed meat is associated with increased risk of

CKD progression and mortality, fruits and vegetable intake were associated with decline in progression of kidney disease.[159-161] Since 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, there is no evidence exist to support different recommendations based on the stage of kidney disease. Thus, current recommendations apply to all non-dialysis CKD population and a practice point provides guidance for those on dialysis. Overall, these recommendations are also similar to the KDIGO 2012 CKD guidelines and the upcoming 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) nutrition guidelines.[162, 163]

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)/day.

Dialysis has long been known to cause a catabolic response. Amino acid losses on both hemodialysis, and particularly peritoneal dialysis, are well documented. Uremia itself causes depressed appetite, increased catabolism and decreased muscle mass.[164] Recommendations for these patients are based on nitrogen balance studies, presence of uremia and malnutrition.[165] Additionally, a slightly higher protein intake in patients with diabetes may help avoid hypoglycemia, given their decreased ability for gluconeogenesis. This practice point mirrors guidelines of the upcoming 2020 KDOQI nutrition guidelines.[163]

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 2g of sodium per day (90 mmol of sodium per day or 5g of sodium chloride per day) improves blood pressure and is associated with lower cardiovascular risk for the general population.[166] 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.

Key information

Balance of benefits to 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.[166, 167] Population based studies have reported that sodium consumption above a reference level of 2 g per day 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 renin-angiotensin system blockers.

The US National Academy of Sciences group found 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 1,500 to 2,300 mg/day was not linked to any harm, finding "Insufficient evidence of adverse health effects at low levels of intake".[168]

People with orthostatic hypotension may need their sodium intake to be guided by their healthcare provider, just as in some rare cases with excessive sodium sweat 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 greater than five grams sodium per day, may need to specifically discuss their salt intake with their treating physician.

Quality of evidence

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

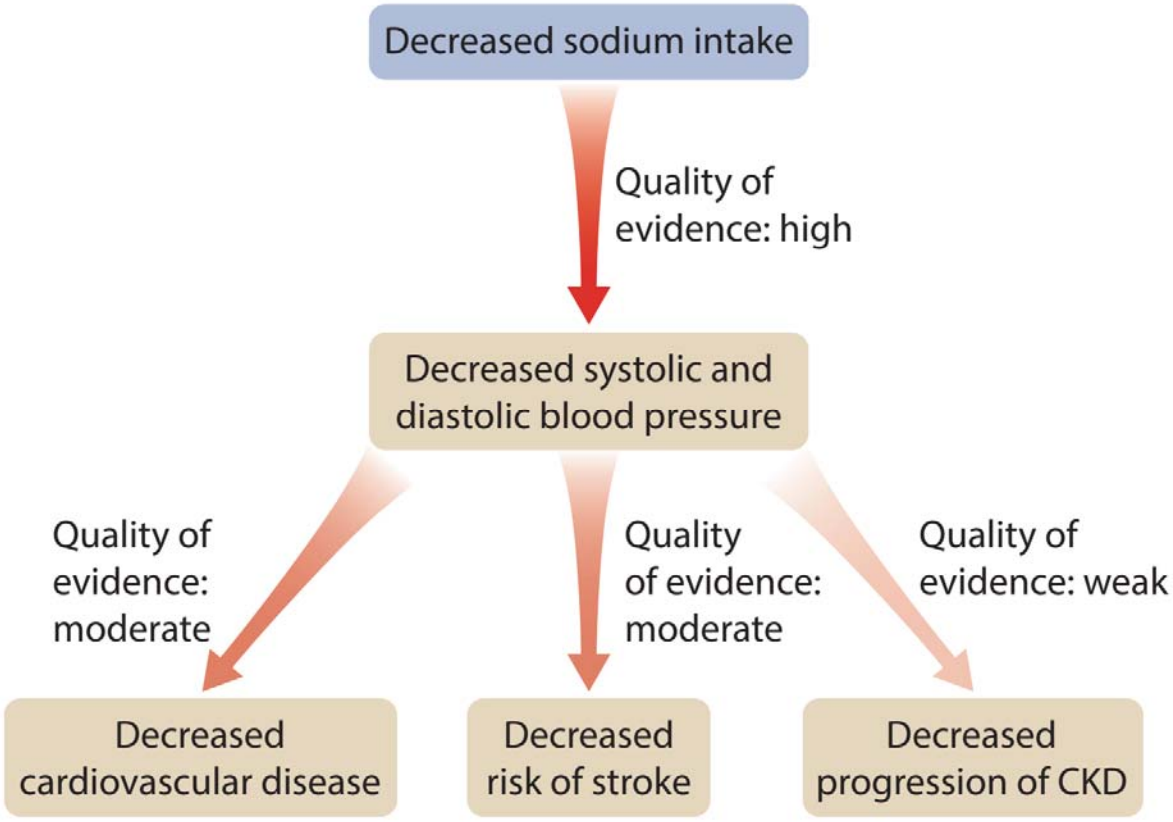
Fifteen relevant studies were identified comparing low salt versus normal salt diets in several groups (Table S13 – S16).[161, 169-183] All studies contained small numbers of patients and examined surrogate outcomes, with the certainty of the evidence being low due to risk of bias and inconsistency or imprecision. "Long-term" studies had a mean follow up of five weeks and "short-term" studies had a mean follow up of six days

Almost all studies investigating nutritional interventions in kidney disease stem from epidemiological and/or small retrospective studies and these studies are generally rated as low quality of the 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. Nutritional changes and modifications to intake typically take long periods to effect change and require months and years to see results. Often studies, due to financial constraints, 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 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.[163, 168] The data was insufficient for cardiovascular mortality and kidney disease. There is moderate to high certainty of the 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 7)

Figure 7. Effects of decreased sodium intake on various outcomes and accompanying quality of evidence[185]



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 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 to decrease other unwanted outcomes. It is possible to decrease a person's taste threshold for sodium in about 4-6 weeks, since the taste for salty foods is learned, not inherent.

Some individuals may not have adequate income, cooking ability, or good 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 the patient and family, focusing on real, practical changes patients can make may enable patients to choose a successful nutritional therapy for them. Many individuals may willingly trade moderating their oral intake for the ability to avoid costly medications or unwanted side effects, but some people will be unwilling or unable to make these changes and will need other solutions.

Resource use and costs

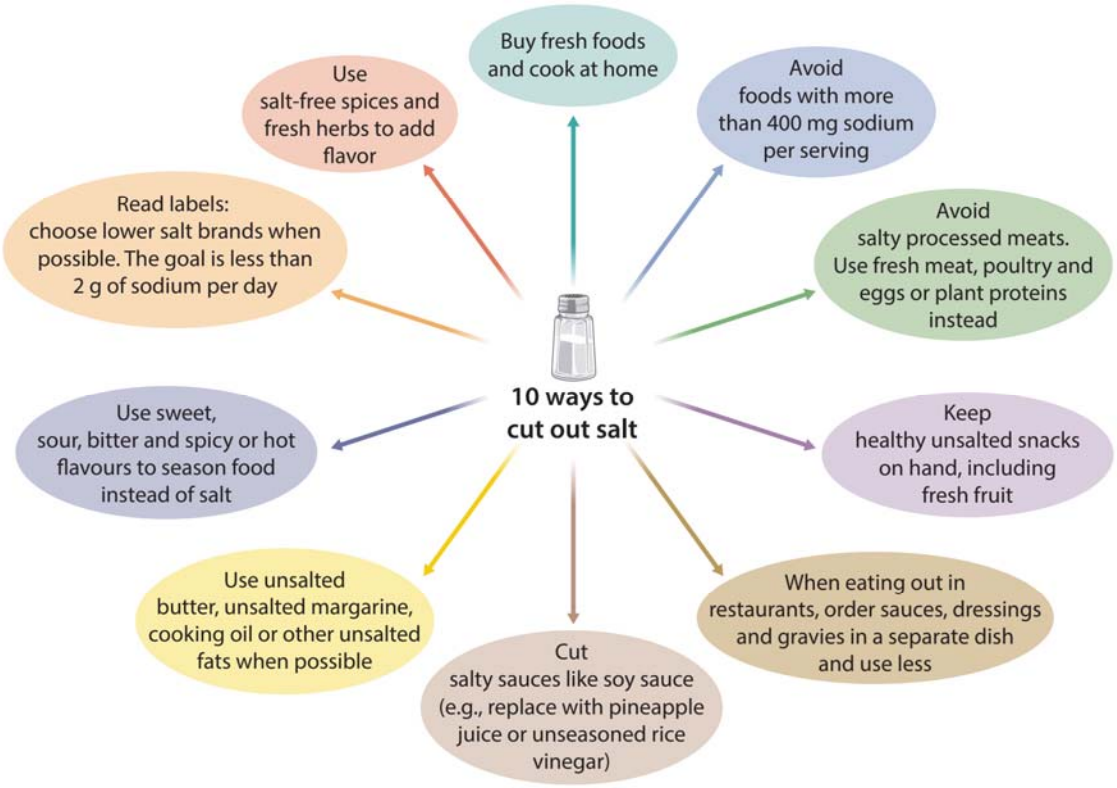
Implementation of these recommendations for people with diabetes and CKD is feasible even in countries with limited resources and should be potentially cost-effective, possibly delaying or postponing the need for medications or more complex and costly kidney replacement therapies such as dialysis and/or transplant, leading to health care savings. Involvement and collaboration with local governmental agencies and their policies and 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 adaption 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. (Figure 8) The DASH-type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with later stage CKD. There is no evidence to suggest that this recommendation should vary based on patient age or sex.

Figure 8. Ten ways to cut out salt



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 improve volume status of the patient along with reducing proteinuria.[184] Clinical studies have also demonstrated that dietary sodium restriction might augment the effects of diuretics and RAAS 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/day. 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, have more difficulty in making the requisite dietary changes, or who find food markedly less palatable after sodium restriction will 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 three million deaths, and 70 million disability adjusted life years (DALYs), a low intake of whole grains caused three million deaths, and 82 million DALYs and low intake of fruits caused two million deaths and 65 million DALYs.[166, 185] This analysis noted that those risks held true regardless of 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 stage of kidney disease.

The US National Academy of Sciences, Engineering, and Medicine recently released *Dietary Intakes for Sodium and Potassium*[163, 168] indicate 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 1,525 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 1,500mg/day for all age groups 14 and over. For those with intakes above 2,300 mg the recommendation is to decrease intake." Larger effects in BP reduction were seen in people with hypertension, but the benefits of sodium reduction were deemed to be applicable to both normotensive and hypertensive people.

Practice Point 3.1.3. Shared decision-making should be a cornerstone of nutritional 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 differences in individuals such as age, dentition, cultural food preferences, finances, patient goals, and to help align their often-conflicting comorbid nutritional 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 have input and offer their own solutions, outcomes are more positive for both patient and provider.[186] 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 patient's family and/or caregivers is also highly desirable. Care must be collaborative, involving all providers, including the primary care provider, and allow for informed decision making by the patient and often their family.

Practice Point 3.1.4. Professional nutritionists, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the nutritional 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 health care providers who can provide information, based on the best adult education techniques available, to allow patients to make informed decisions about their nutritional intake, using shared decision-making techniques. It is quite possible the physician in these situations has not 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 accept or discard. After trial, the patient must be able to return and discuss other options if the original strategies were not satisfactory. In these cases, referral to a diabetes educator, nutrition professional, registered dietitian, or community health nurse would be desirable.

As healthcare systems vary around the world, effort should be place on increasing cost-effective peer coaches or community health 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 education session with health providers, whether they be village health workers, telehealth providers, physicians, nurses, nutrition professionals, or registered dietitians.

In situations where such nutrition education professionals are unavailable or unaffordable, other modes of patient support should be investigated. Peer counselors, village, or community health care 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 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 data base information along with education about how to access and utilize these technologies will help empower patients.

Practice Point 3.1.5. Health care providers should consider cultural differences, intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to the patient and their family.

Giving up foods which bring pleasure is a difficult and often painful adjustment. Often acceptable alternatives exist at the national and 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 a knowledge of acceptable alternatives, methods of preparation, and the cost 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, 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 the patient may translate into lower cost, as well as healthier eating for his/her whole family, 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 nutritional education and dietary modification such as shared decision making, behavior modification techniques, 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 health workers, peer counselors, and other non-traditional health care workers in situations where utilization of more traditional health care positions are 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 relates very much to observational studies in the general population and it has been suggested in heart failure and observational studies of T1D with CKD,[187] that salt restriction is not necessarily beneficial possibly because of concomitant medication including RAAS blockade and diuretics. This might warrant a long-term study looking at the interaction between sodium restriction and medication in diabetes and CKD.

3.2. Physical activity

Recommendation 3.2.1. We recommend that patients with diabetes and CKD should 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 from 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.

Key information

Balance of benefits and harms

Various health benefits of engaging in regular physical activity are well-known.[75, 188] Patients with diabetes and CKD have lower levels of physical activity along with reduced overall fitness levels as compared to the general population.[189] In fact, over two-thirds of adults with CKD in the US do not meet the physical activity levels recommended by the AHA and American College of Sports Medicine.[189, 190] Both in the general population and those with CKD, lower levels of physical activity and physical fitness are associated with progressively higher risks of atherosclerotic CVD and mortality.[191, 192] 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.[188] In the general population and in those with diabetes, improvement in physical activity levels offers cardiometabolic, kidney, and cognitive benefits.[75, 188, 193] Further, evidence suggests overall well-being and better quality of life among those engaging in regular physical activity along with a dose-dependent effect. Similar benefits are anticipated in those with CKD and diabetes who engage in physical activity regularly. However, CKD patients are often older and are at increased risk of falls.[194] They also have functional limitations which might preclude participating in regular exercise and high-intensity activities.[195, 196] 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.

Quality of evidence

Evidence supporting physical activity in people with CKD stem from epidemiological 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.[197]

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, ESKD, and cardiovascular events, and have mainly reported surrogate clinical outcomes. The certainty of the evidence for RCTs comparing a combination of aerobic and resistance training interventions in combination with diet compared with diet alone was low because of study limitations (unclear blinding of outcome assessors) and imprecision (only one study) (Table S17).[198, 199] One trial compared aerobic exercise along with standard of care with standard of care/medical management only and the certainty of the evidence was low due to study limitations (unclear blinding of participants/investigators and outcome assessors) and imprecision (only one study) for critical outcomes blood pressure and very low for kidney function outcomes because of risk of bias and very serious imprecision (only one study, very wide confidence intervals indicating appreciable benefit and harms) (Table S18).[198, 200] The evidence that support these clinical recommendations is indirect as it is mostly based on systematic reviews of RCTs that included both people with and without diabetes, and with and without CKD[17] 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 have to 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 other costs

Implementation of interventions to improve physical activity (such as walking, running, biking, etc.) is feasible even in countries with limited resources and potentially cost-effective.[200] 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 population and also seek assistance from other health care 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 health care providers before engaging in high-intensity activities. Benefits of engaging in routine physical activity is similar among men and women and unlikely to differ based on race or

ethnicity. Overall, these recommendations are similar to the 2012 KDIGO CKD guidelines[201] and the recently released ACC/AHA guidelines on the primary prevention of CVD,[75] 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 (Table 5).

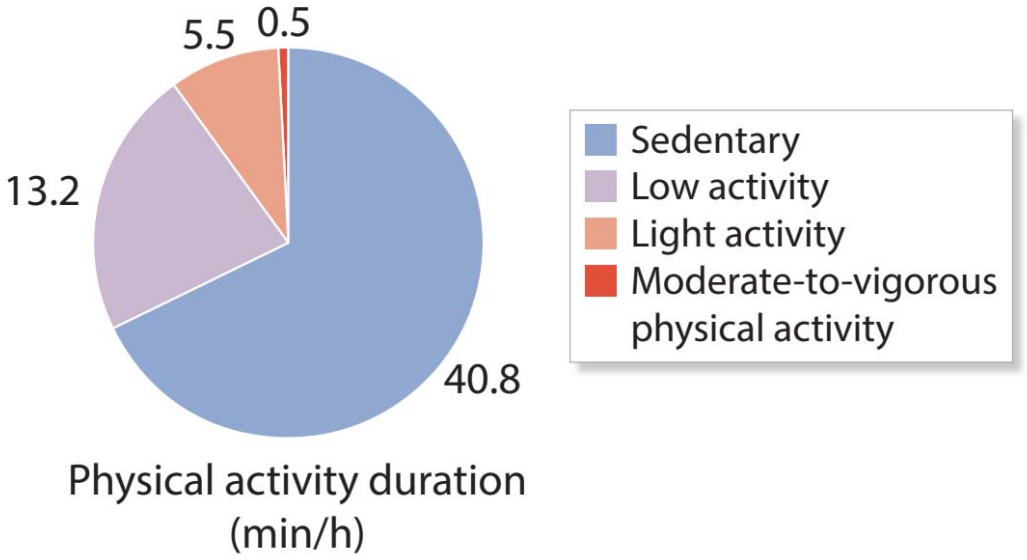
Table 5. Examples of various levels of physical activity and their associated metabolic equivalent (MET)

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

* A metabolic equivalent, or MET, is a unit useful for describing the energy expenditure of a specific activity. MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest.

Data from the World Health Organization indicates 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 arguing for efforts to address this issue across the world.[202] 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 continue to decline.[195] Notably, over two-thirds of adults with CKD do not meet the minimum recommended goal of physical activity (450-750 metabolic equivalents/min/week).[189, 190] (Figure 9) This worsens as kidney function decline, which per se leads to reduced functional capacity. To further complicate this, sedentary behavior is common in CKD, and they spend over two-thirds of the time of the day being sedentary (~40 min/hr).[190] Sedentary behavior is defined as any behavior characterized by an energy expenditure <1.5 metabolic equivalents while in a sitting or reclined position and is associated with a higher risk of hospitalization and death in the general population.[203]

Figure 9. Physical activity levels in people with CKD in the US[190]



Physical activity improves insulin sensitivity, lowers inflammatory markers, and improves endothelial function.[204-206] These, in turn, are associated with an improvement in CVD and all-cause mortality in the general population and those with kidney disease.[207] Higher levels of physical activity are favorably associated with measures of kidney function and damage.[207] In the Nurses Health Study, higher physical activity was associated with lower albuminuria in nondiabetic women. Recent studies have also shown that higher levels of physical activity were associated with a slower decline in eGFR.[207] In the NHANES cohort, physical inactivity was associated with increased mortality risk in CKD and non-CKD populations.[208] Further, a tradeoff of lower sedentary duration with higher light activity duration was associated with a lower hazard of death in the CKD subgroup [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.[188] However, clinical trials examining the benefits of physical activity and exercise in those with CKD are limited.[199] The Look AHEAD study, a large multicenter RCT demonstrated that an intensive lifestyle modification by increasing the physical activity to 175 min/week did not confer cardiovascular benefits among overweight/obese adults with T2D.[209] However, in a secondary analysis of this trial, investigators examined the impact of intensive life style modification on development of high risk CKD defined as a) eGFR <30 ml/min/1.73 m^2 regardless of albumin:creatinine ratio (ACR); b) eGFR <45 ml/min/1.73 m^2 and ACR ≥30 mg albumin/g creatinine; or c) eGFR <60 ml/min/1.73 m^2 and ACR >300 mg/g. Intervention reduced the incidence of the very-high-risk category of CKD by 31% suggesting the long-term benefits of lifestyle changes in those with diabetes and at risk for CKD.[209]

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 exercises. Therefore, physicians and health care 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. While dedicated trials among dialysis patients with diabetes is lacking, few clinical trials have examined home-based and intra-dialytic interventions in those on maintenance dialysis. Simple home-based exercise programs have been shown to be feasible and offer health benefits in those on dialysis.[210] 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.[211, 212]

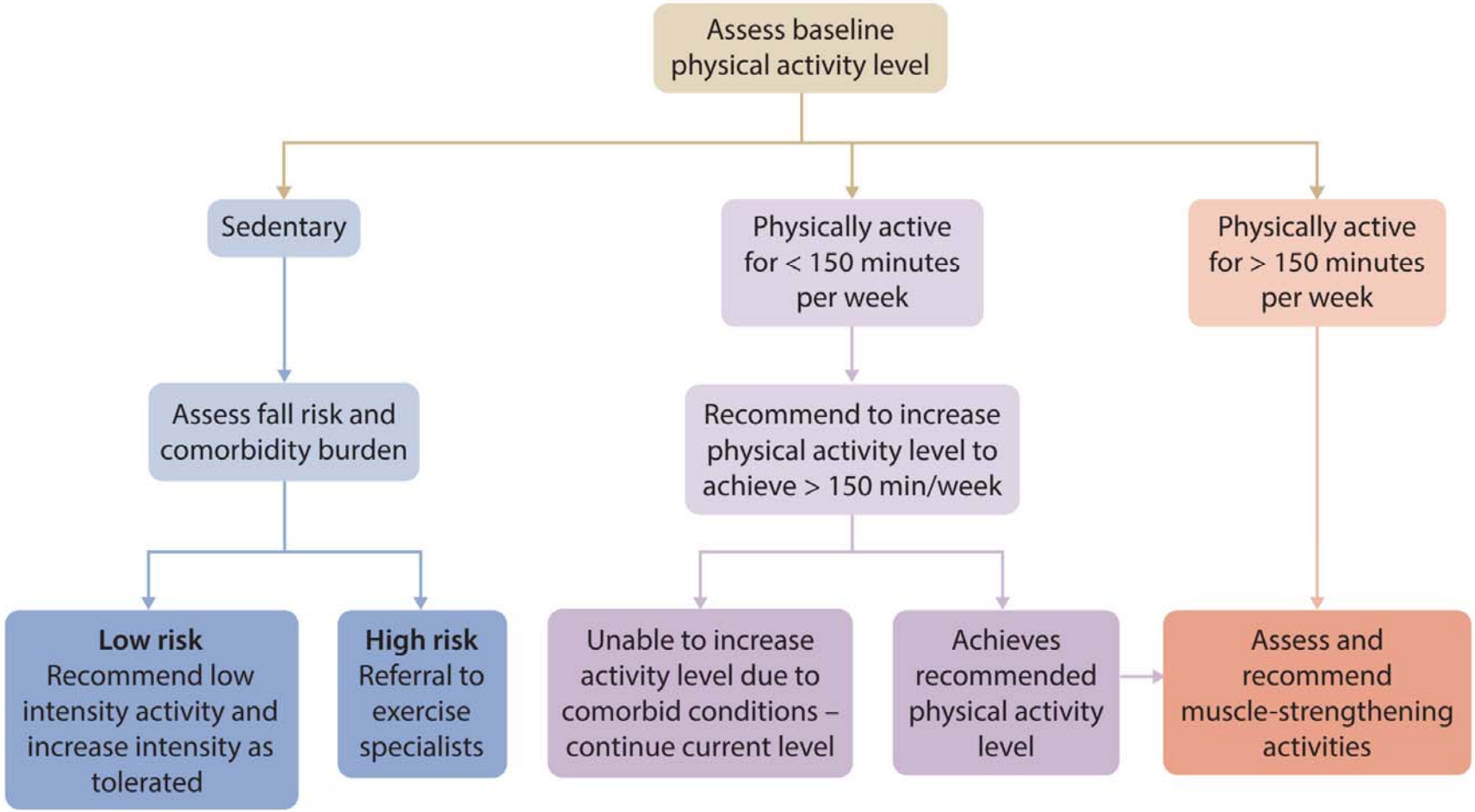
Practice Point 3.2.2. Patients should be advised to avoid sedentary behavior.

CKD patients are often sedentary and also have limited exercise tolerance.[190] They may not able to do longer periods of exercise and should be encouraged to do many short bouts of exercise (less intensity) as they still offer health benefits. Recent data indicate that accumulated amount of activity levels over a week are critical (i.e., even shorter bouts of activities over a week duration yield clinical benefits similar to those accomplished with intense physical activity).[75] Thus, where possible, activity should be spread throughout the week to maximize benefits.

Practice Point 3.2.3. For patients at higher risk of falls, physicians should provide advice on the intensity of physical activity (low, moderate, or vigorous) and type of exercises (aerobic vs. resistance or both).

In those with CKD, sarcopenia is common and related to adverse outcomes. Patients should engage in multicomponent physical activities which includes aerobic and muscle-strengthening activities along with balance training activities as tolerated.[213] (Figure 10) Benefits of muscle strengthening is often under-appreciated and they promote weight maintenance and maintenance of lean body mass while attempting to lose weight. Depending on the availability of resources, referral to a physical activity specialist to guide about the type and amount of physical activity can be considered.

Figure 10. Suggested approach to address physical inactivity and sedentary behavior in CKD



CKD = chronic kidney disease

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/1.73 m^2.

Obesity is an independent risk factor for kidney disease progression and CVD.[214] Current evidence suggest 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.[215, 216] Physicians should assess the interest of patients to lose weight and recommend increasing physical activity and making appropriate dietary modifications in those who are obese, particularly when eGFR is ≥30 ml/min/1.73 m^2.

With eGFR <30 ml/min/1.73 m^2 and ESKD treated with dialysis, patients may spontaneously reduce dietary intake, and malnutrition and wasting are potential concerns. Higher BMI has been associated with better outcomes among patients treated with dialysis, and whether intentional weight loss offer health benefits is unclear in this population.[217] Therefore, depending on individual context, weight loss may not be appropriate for some patients with advanced CKD.

RESEARCH RECOMMENDATIONS

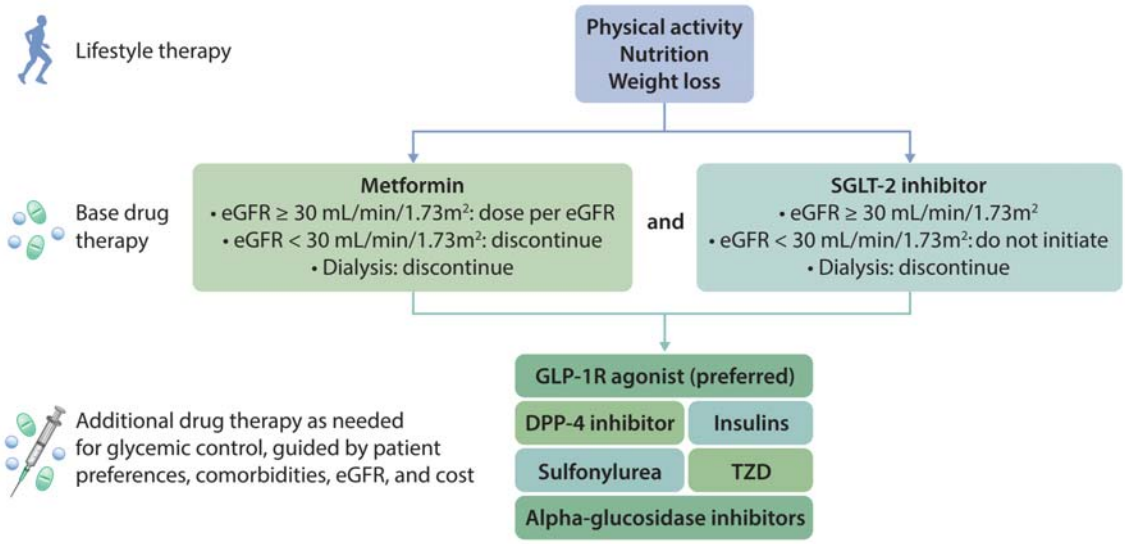
- Further studies should be conducted to compare the benefits and risks of various intensity (light, moderate and vigorous) and types of physical activity levels in those with diabetes and CKD.
- CKD patients are at higher risk of developing sarcopenia, which contributes to adverse outcomes. Resistance 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 undergoing physical activity 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 replacing 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. ANTI-HYPERGLYCEMIC THERAPIES IN PATIENT WITH DIABETES AND CKD

Practice Point 4.1. Glycemic management for patients with Type 2 diabetes and CKD should include lifestyle therapy, base drug therapy with metformin and a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, and additional drug therapy as needed for glycemic control (Figure 11).

Lifestyle therapy is the cornerstone of management for patients with T2D and CKD. In addition, metformin and SGLT-2 inhibitors (SGLT2i) should be used as a base drug therapy that are used in all or nearly all patients with eGFR ≥30 ml/min/1.73 m^2 (Figure 11, Table 6) (see Section 4.1 and 4.2). Additional antihyperglycemic drugs can be added to this base drug therapy as needed to achieve glycemic targets, with GLP-1 RA generally preferred. These recommendations are guided in large part by results of recent large RCTs, summarized in Table 6 and detailed in Sections 4.1, 4.2, and 4.3.

Figure 11. Glycemic treatment algorithm for patients with T2D and CKD



CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1R = glucagon-like peptide-1 receptor; SGLT2 = sodium–glucose cotransporter 2; T2D = type 2 diabetes; TZD = thiazolidinedione

Table 6. Overview of selected large, placebo-controlled clinical outcomes trials assessing the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors

			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/1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR > 300 mg/g and eGFR 30–90 ml/min/1.73 m²	Progression of CKD†	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥ 60 ml/min/1.73 m²	MACE composite of HF and cardiovascular death§	ND/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	↓	ND	None notable
Liraglutide	LEADER	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	ND	GI
Semaglutide	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER-6	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Albiglutide	HARMONY	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	NA	NA	None notable
Dulaglutide	REWIND	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	↓	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥ 15 ml/min/1.73 m²	MACE	ND	↓	ND	HF
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	ND	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥ 15 ml/min/1.73 m²	Progression of CKD†	ND	↓	ND	None notable

↓ = significant reduction in risk, with HR estimate >0.7 and 95% confidence interval not overlapping 1

↓↓ = significant reduction in risk, with HR estimate ≤0.7 and 95% confidence interval not overlapping 1
* Variable composite outcomes that include loss of eGFR, ESKD, and related outcomes
** Progression of CKD defined in CREDENCE as doubling of serum creatinine, ESKD, or death from kidney or cardiovascular causes and in CARMELINA as 40% decline in eGFR, ESKD, or kidney death.
*** Co-primary outcomes
ACR = albumin-creatinine ratio, CKD = chronic kidney disease, CrCl = creatinine clearance, DKA = diabetic ketoacidosis, DPP-4 = dipeptidyl peptidase 4, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease, GFR = glomerular filtration rate, HF = hospitalization for heart failure, GI = gastrointestinal symptoms such as nausea and vomiting, GLP-1 = glucagon-like peptide-1, 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, ND = no significant difference, SGLT2 = sodium–glucose cotransporter 2

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

Both metformin (see Section 4.1) and SGLT2i (see Section 4.2) are preferred medications for patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2. 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 eGFR 30 to 59 ml/min/1.73 m^2, but large effects on reducing CKD progression and CVD.

In most patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2, metformin and SGLT2i can be used safely and effectively together. In fact, the majority of the participants in the SGLT2i cardiovascular outcome trials (CVOTs) were also treated with metformin, and many patients with T2D require more than one antihyperglycemic medication to meet glycemic targets. The combination of metformin and SGLT2i is logical because they have different mechanisms of action, and neither carries increased risk of hypoglycemia.

For patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2 not currently treated with antihyperglycemic drugs (i.e., "drug naïve" patients), there are no high-quality data comparing initiation of antihyperglycemic therapy with metformin first to initiation of SGLT2i first. Given the historical role of metformin as initial drug treatment for T2D, and the fact that most patients in CVOTs treated with SGLT2i were first treated with metformin, it is logical to initiate metformin first for most patients, with the anticipation that SGLT2i will be subsequently added. Initial combination therapy is also a reasonable option when education and monitoring for multiple potential adverse effects is feasible. Using low doses of both SGLT2i and metformin may be a practical approach to manage glycemia, receive the organ protection benefits of SGLT2i (which do not appear to be dose dependent), and minimize drug exposure.

For patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2 who are attaining glycemic targets with metformin as sole antihyperglycemic agent, data supporting use of SGLT2i are limited. Specifically, all participants in the CVOTs for SGLT2i had an HbA1c of at least 6.5%. However, for patients attaining glycemic targets with metformin alone, addition of an SGLT2i (particularly, if both agents are used in low doses) is not likely to cause hypoglycemia and may still provide kidney and cardiovascular benefits. Kidney and cardiovascular benefits are not proven in this specific population but are supported by the observations that SGLT2i reduce kidney and cardiovascular events similarly across the full range of studied HbA1c levels (≥6.5%)[218-223] and that beneficial effects of dapagliflozin on heart failure (among patients with heart failure with reduced ejection fraction) did not require presence of diabetes.[219] More data are needed to confirm or correct this approach in CKD.

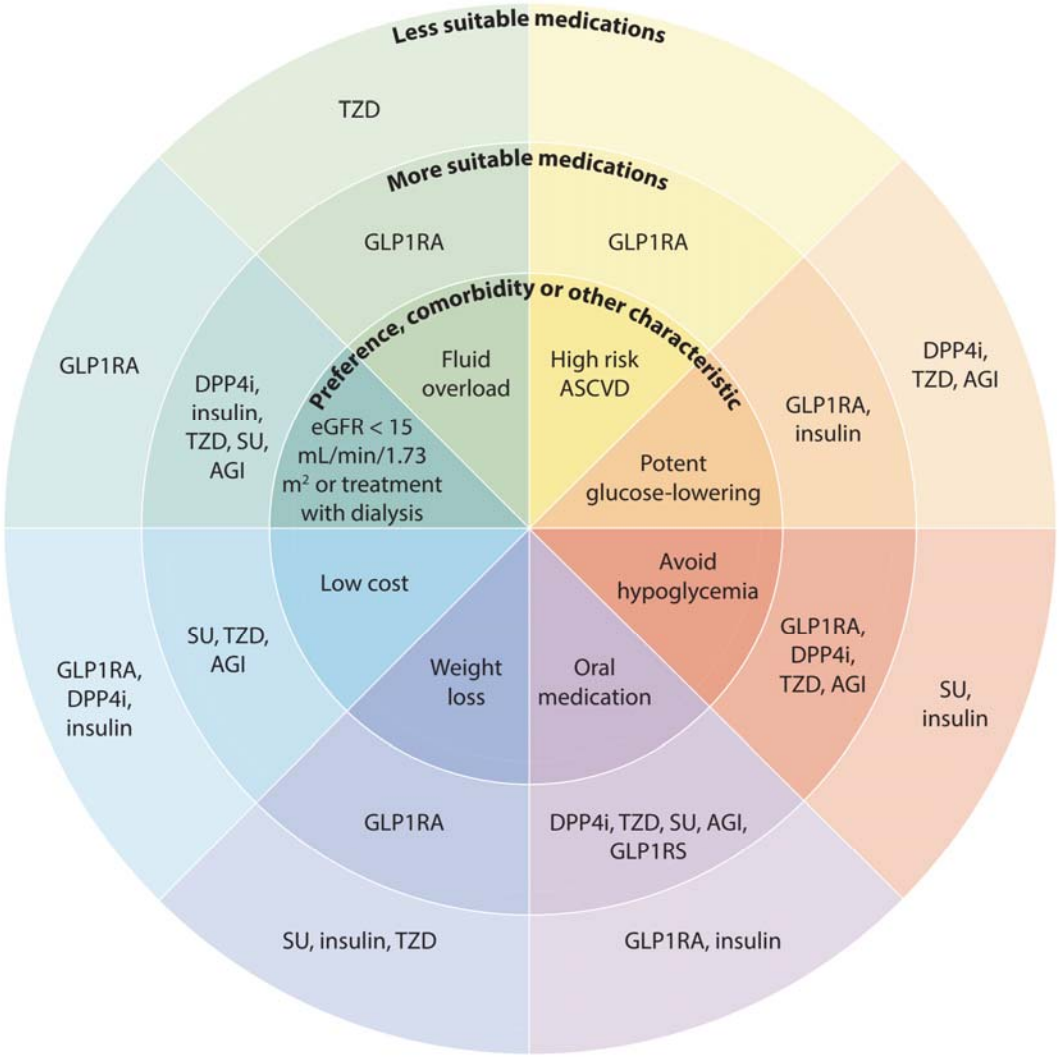
Current evidence suggests that neither metformin or SGLT2i should be initiated in patients with T2D and eGFR <30 ml/min/1.73 m^2 (see Figure 11, Sections 4.1, and Section

4.2). Metformin should be discontinued below an eGFR of 30 ml/min/1.73 m^2. For patients who initiate an SGLT2i at eGFR ≥30 ml/min/1.73 m^2 and subsequently decline to eGFR <30 ml/min/1.73 m^2, SGLT2i can be continued, following the approach studied in the CREDENCE trial.

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 (GLP-1) receptor agonists generally preferred.

Some patients with T2D and eGFR ≥30 ml/min/1.73 m^2 will not achieve glycemic targets with lifestyle therapy, metformin, and SGLT2i; or will not be able to use these interventions due to intolerances or other restrictions. In addition, initiation of these drugs is not recommended for patients with eGFR <30 ml/min/1.73 m^2. Antihyperglycemic agents other than metformin and SGLT2i will likely be needed in these situations. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are generally preferred because of their demonstrated cardiovascular benefits, particularly among patients with established atherosclerotic cardiovascular disease (ASCVD), and possible kidney benefits (see Section 4.3). Other classes of antihyperglycemics may also be used, considering the patient factors detailed in Figure 12. Dipeptidyl peptidase-4 (DPP-4) inhibitors lower blood glucose with low risk of hypoglycemia but have not been shown to improve kidney or cardiovascular outcomes.[224] All antihyperglycemic medications should be selected and dosed according to eGFR.[225] For example, sulfonylureas that are long-acting or cleared by the kidney should be avoided at low eGFR.

Figure 12. Patient factors influencing selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD



ASCVD = atherosclerotic cardiovascular disease, AGI = alpha glucosidase inhibitor, CKD = chronic kidney disease, DPP-4i = dipeptidyl peptidase 4 inhibitor, eGFR = estimated glomerular filtration rate, GLP-1RA = glucagon-like peptide-1 receptor agonist, SU = sulfonylurea, T2D = type 2 diabetes, TZD = thiazolidinedione

4.1. Metformin

Recommendation 4.1.1. In patients with Type 2 diabetes, CKD, and eGFR ≥30 ml/min/1.73 m^2, we recommend that metformin be used as the first-line treatment for hyperglycemia *(1B)*.

This recommendation places a high value on the efficacy of metformin in lowering HbA1c, its widespread availability and low cost, good safety profile and its potential benefits in preventing weight gain and cardiovascular protection; and 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 anti-glycemic 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 in patients with chronic kidney disease (CKD). The United Kingdom Prospective Diabetes Study (UKPDS) study showed that metformin monotherapy in obese individuals achieved similar reduction in HbA1c levels and fasting plasma glucose levels, with lower risk for hypoglycemia when compared to those given sulfonylureas or insulin.[226] Moreover, a systematic review demonstrated that metformin monotherapy was comparable to thiazolinediones (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, -0.31).[227, 228] This was with 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)] comparing metformin to sulfonylureas) and impaired kidney function [OR 0.17 (95% CI 0.11, 0.26)] comparing metformin to sulfonylureas).[228]

In addition to its efficacy as an anti-glycemic agent, studies have demonstrated that treatment with metformin is effective in preventing weight gain and may achieve weight reduction 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 three-year study period while the body weight increased significantly with sulfonylurea and insulin treatment.[226] Similarly, this effect was reproduced in an analysis of a subgroup of patients in the UKPDS study who failed diet therapy and subsequently randomized to metformin, sulphonylurea or insulin therapy, with patients allocated to the metformin group having the least amount of weight gain.[119] Likewise, the same systematic review earlier showed that metformin treatment had greater weight reduction when compared to sulfonylurea [-2.7 kg (95% CI -3.5, -1.9)], thiazolinediones [-2.6 kg (95% CI -4.1, -1.2)] or DPP-4 inhibitors [-1.3 kg (95% CI -1.6, -1.0)].[227, 228]

In addition, treatment of 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, metformin had a greater effect than sulfonlyureas or insulin for reduction in diabetes-related endpoint, which included death from fatal or non-fatal myocardial infarction, angina, heart failure or stroke.[119] An RCT, the SPREAD-DIMCAD study, performed in China 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 five years.[229] Indeed, in a systematic review performed, the signal for the reduction in cardiovascular mortality was again detected, with RR of 0.6-0.7 from RCTs in favor of metformin compared with sulfonylureas.[228]

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.[228] 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).[119]

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of about five hours.[230] 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 its use in CKD where the drug excretion may be impaired, thereby increasing the risk of lactic acid accumulation.[231] However, the association between metformin and lactic acidosis had been inconsistent, with literature reviews even refuting this concern,[232] including in patients with eGFR 30 to 60 ml/min/1.73 m^2.[233] 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 eGFR ≥30 ml/min/1.73 m^2 .[24]

While the effect of cardioprotection with metformin use are studied mainly in the general population, evidence of this benefit in patients with CKD, especially those with reduced eGFR, are less consistent. A systematic review considered the association of all-cause mortality and major adverse cardiovascular events (MACE) with treatment regimens that included metformin in patient populations where metformin use is traditionally taken with precautions.[235] There were no RCT, 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 [hazard ratio (HR) 0.78, (95% CI 0.63, 0.96)], while there was no difference in MACE-related diagnoses with metformin use in one 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)]. While the signal for cardioprotection 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 with metformin treatment in patients with reduced eGFR.

Quality of the 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 benefit of weight reduction compared to insulin and sulfonylurea was also assessed by the Work Group to be an important consideration, and patients who are patients value weight reduction would be prefer treated with metformin compared to 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.

Resources and other costs

Metformin is among the least expensive anti-glycemic medications available 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 is currently no safety data for metformin use in patients with eGFR <30 ml/min/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/1.73 m^2. These practical issues will be addressed in the practice points.

Different formulations of metformin

Typically, metformin monotherapy has been shown to lower HbA1c by approximately 1.5%.[236, 237] Table 7 outlines the different formulations, and their respective recommended doses, of metformin available.

Table 7. Different formulations of metformin

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

Metformin is generally well-tolerated, though gastrointestinal adverse events may be experience in up to 25% of patients treated with immediate-release form of metformin, with treatment discontinuation occurring in about 5% to 10% of patients.[238-240] 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-blind RCT of adults with T2D who were randomly assigned one of three extended-release metformin treatment regimens (1,500 mg once daily, 1,500 mg twice daily or 2,000 mg once daily) or immediate-release metformin (1,500 mg twice daily), overall

incidence of adverse events was noted to be similar for all treatment groups, though fewer patients in the extended-release developed nausea during the initial dosing period (2.9%, 3.9%, 2.4% for the respective extended-release treatment regimen versus 8.2% in the immediate-release group, p=0.05).[241] Moreover, fewer patients who received the extended-release metformin discontinued because of gastrointestinal side effects during the first week (0.6% versus 4.0%). Another RCT of 532 treatment-naïve Chinese patients with T2D (the CONSENT study), however, showed comparable gastrointestinal adverse events between patient receiving monotherapy with immediate-release or extended-release metformin (23.8% versus 22.3% respectively).[242]

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, benefits with weight reduction and cardiovascular protection, good safety profile, 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 will 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 majority, if not all physicians, will be comfortable in initiating metformin treatment due to the familiarity with this drug and its good safety profile.

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

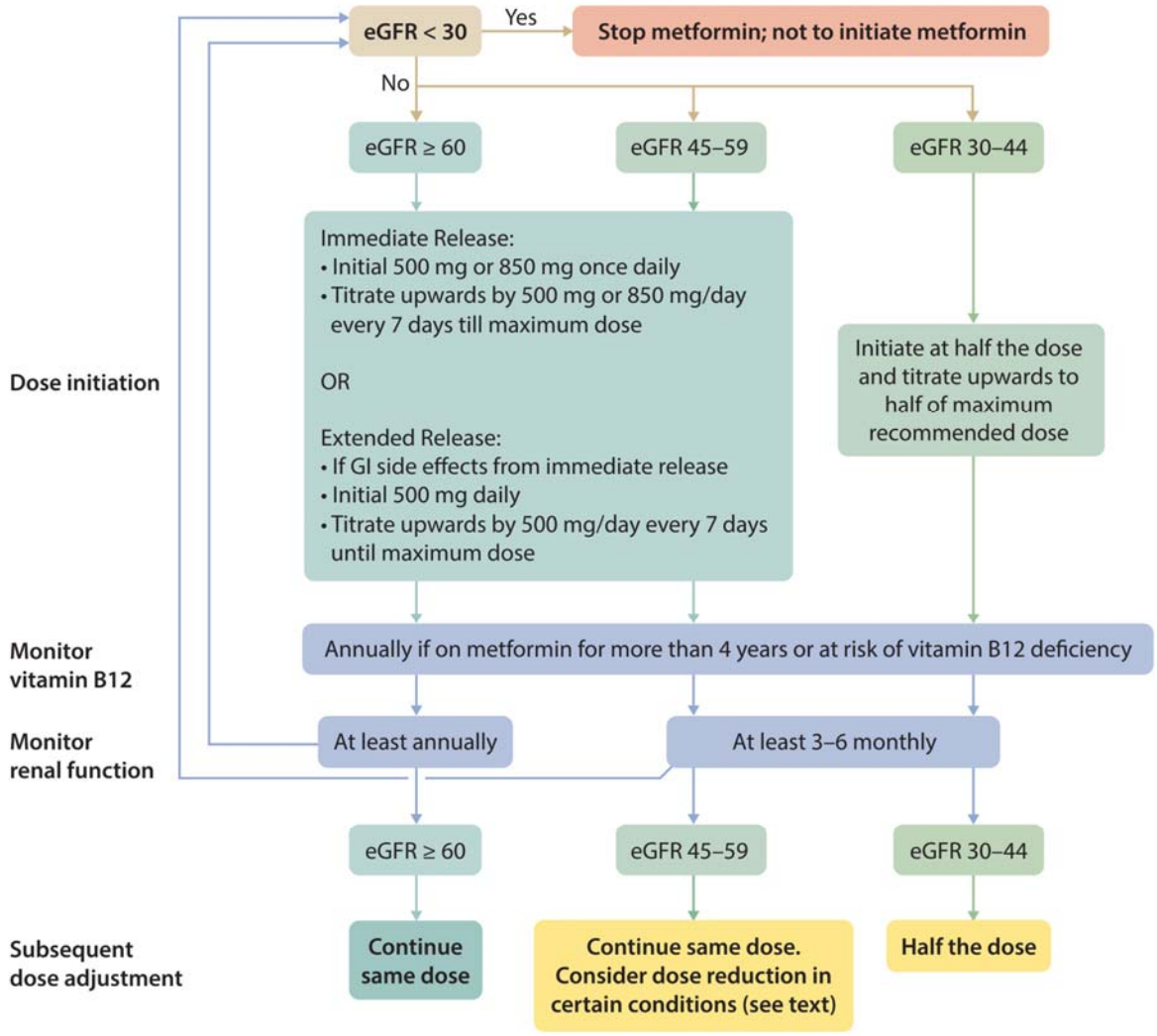
The data for the use of metformin after kidney transplantation is less robust. Most of the evidence was derived from registry and pharmacy claims data which showed that the use of metformin was not associated with worse patient or allograft survival.[243] One such analysis even suggested that metformin treatment after kidney transplantation was associated with significantly lower all-cause, malignancy-related and infection-related mortality.[244] The Transdiab study was a pilot randomized placebo-controlled trial recruited 19 patients with impaired glucose tolerance after kidney transplantation from a single center, which examined the efficacy and tolerability of metformin treatment.[245] While there were no adverse signals from the trial, unfortunately, the number of patients recruited were too small for any conclusive recommendations. In view of the lack of adverse 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 should be based on the eGFR, using the same approach for the CKD group.

Practice Point 4.1.2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is <60 ml/min/1.73 m^2. (Figure 13)

Since 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 eGFR drops below 60 ml/min/1.73 m^2, with a view to decrease the dose accordingly.

Figure 13. Suggested approach in dosing metformin based on the level of kidney function



eGFR, estimated glomerular filtration rate; GI, gastrointestinal

Practice Point 4.1.3. Adjust the dose of metformin when eGFR is less than 60 ml/min/1.73 m^2. (Figure 13)

Figure 13 provides a suggested approach in adjusting the dose for metformin in accordance to the decline in the kidney function:

- Generally, dose adjustment is not necessary for eGFR greater than 45 ml/min/1.73 m^2.
- For eGFR between 45 and 59 ml/min/1.73 m^2, dose reduction may be considered in the presence of conditions that predispose to hypoperfusion and hypoxemia. Maximum dose should be halved when the eGFR declines to between 30 to 45 ml/min/1.73 m^2.
- Treatment discontinued when the eGFR declines to below 30 ml/min/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 four years.

Metformin interferes with intestinal vitamin B12 absorption, and the National Health and Nutrition Examination Survey (NHANES) study found that biochemical vitamin B12 deficiency was noted in 5.8% of patients with diabetes on metformin, compared to 2.4% ($p = 0.0026$) in those not on metformin and 3.3% ($p = 0.0002$) in patients without diabetes.[246] 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.[247] Metformin treatment was associated with a mean reduction of vitamin B12 concentration compared to placebo after approximately four years. While that is the case, clinical consequences of vitamin B12 deficiency with metformin treatment is uncommon, and it is the judgment of the Work Group that routine concurrent supplementation with vitamin B12 is unnecessary. In addition, the study also demonstrated that the reduction in vitamin B12 concentration is increased with time of metformin therapy, and monitoring of vitamin B12 levels should be considered in patients who have been on long-term metformin treatment (e.g., for more than four years, or in those who are 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 Type 2 diabetes with CKD, including those with eGFR less than 30 ml/min/1.73 m^2 or on dialysis.
- RCTs are needed to evaluate the safety and efficacy of metformin in kidney transplant recipients

4.2 Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

Background

Patients with T2D and CKD are at increased risk of both cardiovascular events and progression to ESKD. Thus, preventive treatment strategies that reduce both the risk of adverse kidney and cardiovascular outcomes are paramount. There is substantial evidence confirming that sodium-glucose cotransporter-2 inhibitors (SGLT2i) confer significant kidney-protective and cardioprotective effects in these patients. This was demonstrated in: 1) three large RCTs (e.g., EMPA-REG, CANagliflozin cardioVascular Assessment Study (CANVAS), and DECLARE)[220, 222, 223] reporting on efficacy for primary cardiovascular outcomes but also reported on secondary kidney outcomes; 2) a meta-analysis of these three CVOTs which stratified by CKD subgroups;[248] 3) an RCT (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)) specifically designed to evaluate kidney outcomes as the primary outcome;[221] 4) a meta-analysis of four trials (EMPA-REG, CANVAS, CREDENCE, DECLARE) evaluating kidney outcomes,[249] and 5) an RCT evaluating the primary outcome of heart failure/cardiovascular death, among adults with reduced ejection fraction with and without diabetes, and also stratified by eGFR (<60 and ≥60 ml/min/1.73 m^2).[219] (Table 8)

SGLT2i lower blood glucose levels by inhibiting kidney tubular reabsorption of glucose. They also have a diuretic effect as the induced glycosuria leads to an osmotic diuresis and increased urine output. SGLT2i also appear to alter fuel metabolism, shifting away from carbohydrate utilization to ketogenesis. In RCTs, SGLT2i confer modest lowering of HbA1c (0.3-0.6%), systolic blood pressure (3-4 mm Hg), diastolic blood pressure (1-2 mm Hg) and weight loss (0.8-2.0 kg). 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 intra-glomerular pressure and single-nephron hyperfiltration leading to preservation of kidney function.[250] Currently, the safety and efficacy of SGLT2i have not yet been demonstrated for people with eGFR <30 ml/min/1.73 m^2, in kidney transplant recipients, or among individuals with T1D; further studies will help clarify the kidney and cardiovascular benefits among these subgroups.

Recommendation 4.2.1. In patients with Type 2 diabetes, CKD, and eGFR ≥30 ml/min/1.73 m^2, we recommend including an SGLT-2 inhibitor (SGLT2i) in the antihyperglycemic treatment regimen *(1A)*.

This recommendation places a high value on the kidney-protective and cardioprotective effects of 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 SGLT2i.

Key information

Balance of benefits and harms

Cardiovascular outcomes

The EMPA-REG trial enrolled over 7,000 patients with T2D, baseline glycated hemoglobin (HbA1c) of 7-10%, established CVD (almost 100%), and eGFR of at least 30 ml/min/1.73 m^2. [223] Of these, 1819 (25.9%) participants had eGFR <60 ml/min/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 three-point MACE by 14% [HR 0.86 (95% CI 0.74, 0.99)].

Among participants in EMPA-REG with eGFR 30 to 60 ml/min/1.73 m^2, there was a trend for benefit for the primary cardiovascular outcome that was not statistically significant in this subgroup, but importantly there was no evidence for heterogeneity of treatment effect across all eGFR subgroups (p-interaction = 0.20). In a pre-specified analysis from EMPA-REG of patients with prevalent kidney disease defined as eGFR <60 ml/min/1.73 m^2 and/or ACR >300 mg/g, 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)].[251]

The CANVAS program, which combined data from two RCTs (CANVAS and CANVAS-R) enrolled over 10,000 patients with T2D, HbA1c between 7.0-10.5%, and eGFR of at least 30 ml/min/1.73 m^2. [220] Approximately two-thirds (66%) of participants had established CVD and 2,039 (20.1%) had CKD with an eGFR <60 ml/min/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. Similar to EMPA-REG, the SGLT2i canagliflozin also reduced MACE by 14% [HR 0.86 (95% CI 0.75, 0.97)].

In subgroup analyses from CANVAS, those with eGFR 30 to 60 ml/min/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 HbA1c 6.5 to 12%. Only 41% had established cardiovascular disease, the other 59% had multiple cardiovascular risk factors, so it was largely a primary prevention trial.[222] Although creatinine clearance of ≥60 ml/min was an eligibility criterion, there were 1,265 participants (7.4%) who had an eGFR <60 ml/min/1.73 m^2. Participants were randomized to dapagliflozin 10 mg per day versus placebo and followed for median of 4.2 years. In the main trial, dapagliflozin did not reduce the primary safety outcome of composite MACE but did reduce a co-primary efficacy outcome of cardiovascular death or hospitalization for heart failure. 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).

In the CREDENCE trial among patients with T2D with CKD (discussed further below), 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.[221]

The number of participants with T2D and CKD (eGFR 30 to <60 ml/min/1.73 m^2) and 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 trials and examined cardiovascular outcomes among individuals with and without CKD.[248] For those trial participants with eGFR 30 to <60 ml/min/1.73 m^2, 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)].

Heart failure outcomes

Notably, the significant reduction in risk of hospitalizations for heart failure was consistent across all three trials [EMPA-REG, CANVAS, and DECLARE]. This 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.[252]

The DAPA-HF trial enrolled 4,744 patients with symptomatic heart failure with reduced ejection fraction (HFrEF) defined as EF ≤40%, with eGFR ≥30 ml/min/1.73 m^2 (mean eGFR 66 ml/min/1.73 m^2), including 55% of individuals without diabetes.[219] 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 dapaglifozin group and 21.2% of placebo group

[HR 0.74 (95% CI 0.65, 0.85)]. The primary outcome was similarly reduced for individuals with and without diabetes with no effect heterogeneity by diabetes status. The primary outcome was also similar among those with eGFR ≥60 ml/min/1.73 m^2 [HR 0.76 (95% CI 0.63, 0.92)] and <60 ml/min/1.73 m^2 [HR 0.72 (95% CI 0.59, 0.86)]. This suggests a potential role for cardiovascular benefit among CKD patients with HFrEF, even without the presence of diabetes.

Kidney outcomes

EMPA-REG (empagliflozin versus placebo) also evaluated a pre-specified kidney outcome of incident or worsening nephropathy, defined as progression to severely increased albuminuria (ACR >300 mg/g or 30 mg/mmol), doubling of serum creatinine accompanied by eGFR ≤45 ml/min/1.73 m^2, initiation of kidney replacement therapy or kidney death. This incident or worsening nephropathy outcome was lower in the empagliflozin group, 12.7% versus 18.8%, with HR of 0.61 (95% CI 0.53, 0.70).[250]

In the CANVAS program (overall cohort including those with and without baseline CKD), canagliflozin also conferred kidney benefit with a 37% 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)]. The CANVAS program further reported additional pre-specified kidney outcomes.[253] The composite kidney outcome of doubling of serum creatinine, ESKD, 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.[253]

In the DECLARE trial (dapagliflozin versus placebo), there was a 1.3% absolute and 24% relative risk reduction in the secondary kidney outcome [a composite of ≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESKD, cardiovascular, or kidney death: HR 0.76 (95% CI 0.67, 0.87)].[222] In DAPA-HF, the secondary outcome of worsening kidney function (defined as ≥50% reduction in eGFR, ESKD, or kidney death), occurred in 1.2% of dapagliflozin arm and 1.6% of placebo arm [HR 0.71 (95% CI 0.44, 1.16)], which was not statistically significant (p = 0.17).[219] However, the median duration of the DAPA-HF trial was only 18 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 trials and examined kidney outcomes among individuals with and without CKD.[248] For those trial participants with eGFR 30 to <60 ml/min/1.73 m^2, SGLT2i reduced the risk of adverse kidney outcomes (composite worsening kidney failure, ESKD, or kidney death) [HR 0.67 (95% CI 0.51, 0.89)].

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.[248]

This was addressed in the CREDENCE trial, which was the first RCT of an SGLT2i specifically powered for primary kidney outcomes among patients exclusively with albuminuric CKD.[221] CREDENCE enrolled patients with T2D (with HbA1c of 6.5%-12.0%) and CKD, defined by eGFR 30 to 90 ml/min/1.73 m^2 with albuminuria (ACR of 300 to 5000 mg/g), who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB. In CREDENCE, 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 ESKD, 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, 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 kidney death, 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 non-significant).

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.[221, 250, 253, 254] An updated 2019 meta-analysis pooled data from the four major RCTs of SGLT2i that evaluated major kidney outcomes (EMPA-REG, CAVAS, CREDENCE, and DECLARE).[249] This analysis that included nearly 39,000 participants with T2D, found that SGLT2i significantly reduced the risk of dialysis, kidney transplant, or kidney death by 33% [RR 0.67 (95% CI 0.52, 0.86)]. There was also reduction in ESKD and acute kidney injury (AKI). The benefits of SGLT2i on kidney outcomes were seen across all eGFR subgroup including those with eGFR 30 to 45 ml/min/1.73 m^2. [249]

Table 8. Cardiovascular and kidney outcome trials for SGLT2 inhibitors

	EMPA-REG	CANVAS	DECLARE	CREDENCE	DAPA-HF
Drug	Empagliflozin 10mg, 25 mg once daily	Canagliflozin 100 mg, 300 mg once daily	Dapagliflozin 10 mg once daily	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once day versus placebo
Total of participants	7,020	10,142	17,160	4,401	4,474
N (%) with T2D	7,020 (100%)	10,142 (100%)	17,160 (100%)	4,401 (100%)	2,139 (45%)
N (%) with CVD	7,020 (100%)	6,656 (66%)	6,974 (41%)	2220 (50%)	4,474 (100%) with HFrEF
eGFR criteria for enrollment	≥ 30 mL/min/1.73m^2	≥ 30 mL/min/1.73m^2	CrCl ≥ 60 mL/min, 45% had eGFR 60–90	30–90 mL/min/1.73m^2, ACR <300–5000 mg/g	≥ 30 mL/min/1.73m^2
Mean eGFR at enrollment (mL/min/1.73m^2)	74	76	85	56	66
N (%) with eGFR < 60	1,819 (26%)	2,039 (20%)	1,265 (7.4%)	40%	1926 (41%)
ACR	No criteria. ACR <30 mg/g in 60%; 30-300 mg/g in 30%; >300 mg/g in 10%	No criteria. Median ACR 12.3 mg/g	No criteria	Median ACR 927 mg/g	
Follow-up (median, yrs)	3.1	2.4	4.2		1.5
Primary outcome	MACE	MACE	MACE	Composite kidney	CV death, HF hospitalization, urgent HF
CV outcome results	MACE: [HR 0.86 (0.74, 0.99)]; hospitalization for HF [HR 0.65 (0.50, 0.85)]	MACE: [HR 0.86 (0.75, 0.97); hospitalizations for HF [HR 0.67 (0.52, 0.87)	MACE [0.93; 0.84, 1.03)]; CV death or hospitalization fo HF [HR 0.83 (0.73, 0.95)]	CV death, MI, stroke: [HR 0.80 (0.67, 0.95)]; Hospitalization for HF: [HR 0.61 (0.47, 0.80)]	Primary: HR 0.74 (95% CI 0.65, 0.85)]
Kidney outcome	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or kidney death) and incident albuminuria	Composite doubling in SCr, ESKD, or death from kidney causes	Composite of ≥ 40% decrease in eGFR to < 60, ESKD, CV or kidney death	Composite of ESKD, doubling SCr, or death from kidney or CV causes	Worsening kidney function (defined as ≥ 50% reduction in eGFR, ESKD, or kidney death)
Kidney outcome results	Incident/worsening nephropathy: 12.7% vs. 18.8% in canagliflozin vs. placebo. [HR 0.61 (0.53, 0.70)] Incident albuminuria: NS	Composite kidney: 1.5 vs. 2.8 1000 patient-years in the canagliflozin vs. placebo; [HR 0.53 (0.33, 0.84)]	Composite kidney [HR 0.76 (0.67, 0.87)	Primary kidney: HR 0.70 (0.59, 0.82)	HR 0.71 (0.44, 1.16), p=0.17

CrCl = creatinine clearance, CV = cardiovascular, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease, GFR = glomerular filtration rate, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, KRT = kidney replacement therapy, MACE = major adverse cardiovascular events, MI = myocardial infarction, NS = not significant, SCr = serum creatinine, SGLT2 = sodium–glucose cotransporter 2, T2D = type 2 diabetes, uACR = urinary albumin-creatinine ratio

Harms

There is an increased risk of diabetic ketoacidosis conferred by SGLT2i, generally affecting up to 1 in 1,000 patients (in CREDENCE this was 2.2 versus 0.2 per 1000 patient-years for canagliflozin versus placebo).[221]

In CANVAS, but not CANVAS-R, there was a higher rate of fractures attributed to canagliflozin.[220] Of note, in CREDENCE which evaluated 100 mg/day of canagliflozin, there was no excess fracture rate.[221]

There is an increased risk of genital mycotic infections with SGLT2i in both men and women that is consistent across all trials. In CREDENCE, which was exclusively conducted in a population of patients with T2D and CKD, this occurred in 2.27% of canagliflozin arm versus 0.59% of placebo.[221] Most of the time such infections can be managed with topical anti-fungal medications.[255]

The increased risk of lower extremity amputations seen with canagliflozin in CANVAS[220] was not reproduced in CREDENCE, even though this trial did implement special attention to foot care for prevention.[221] This risk of amputations was also not seen with other SGLT2i (empagliflozin and dapagliflozin) in the EMPA-REG and DECLARE trials, respectively. 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 due to chance. However, during CREDENCE recruitment, an amendment was introduced excluding those at risk for amputation. In DAPA-HF, major hypoglycemia, lower limb amputation and fracture occurred infrequently and were similar between the two treatment groups.[219] Self-care practices, such as daily bathing, may reduce risk of adverse events such as genital mycotic infections and foot complications.

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 G1 to G3b (eGFR >30 ml/min/1.73 m^2) a pooled meta-analysis of RCTs combining efficacy data for this CKD subset, and a RCT exclusively enrolled patients with T2D and albuminuric CKD. From this data, there is moderate to high quality evidence that SGLT2i reduce undesirable consequences in patients with T2D and CKD, specifically cardiovascular death, hospitalization for heart failure, and progression of CKD. An updated Cochrane systematic review and meta-analysis[256] conducted by the ERT identified high certainty of the evidence for most critical and important outcomes, except for hypoglycemia requiring third party assistance, fractures and HbA1c due to imprecision or study limitations (Table S19).[221, 222, 257-267]

- *Study design:* As discussed, there have now been four RCTs[221, 222, 250, 254] and a meta-analysis of these four trials[249] 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 trial,[221] kidney outcomes were the primary outcome evaluated. Additionally, the ERT identified 13 relevant RCTs[221, 222, 257-267] in an updated Cochrane systematic review.

- *Risk of bias* is low as these RCT studies demonstrated good allocation concealment, adequate blinding, with complete accounting for most patients and outcome events. In the meta-analysis by Zelniker *et al.,*[248] the authors found all three trials met 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, apart from two outcomes, 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.[249]

- *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 one outcome, hypoglycemia requiring third party assistance, because of a few events, well below the required optimal information size.

- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. Additionally, funnel plot assessments indicate no concerns regarding publication bias.

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 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. 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 dehydration, genital infections, or lower extremity amputation due

to foot ulcerations. Older women with history of urinary tract infections may also 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-protective and cardioprotective 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 may choose an alternate medication.

Resource use and costs

While some models have found use of SGLT2i to be a cost-effective strategy among patients with T2D given the cardiovascular outcome benefits,[268, 269] nevertheless, these medications are frequently cost-prohibitive for many patients compared to other cheaper oral diabetes medications (notably sulfonylureas) which do not have same level of evidence for cardiovascular and kidney benefits. In many cases, obtaining reimbursement or pre-authorizations from insurance companies for SGLT2i coverage places undue burden on healthcare professionals and patients. There are disparities in the insurance coverage for these class of medications and individuals' ability to pay at current costs. Availability of drugs also vary between countries and regions. Thus, treatment decisions must take into account patient's preference about the magnitude of benefits and harms of treatment alternatives, drug availability in local country, and cost. Ultimately, some patients may not be able to afford the new medications, and should be guided in making informed decisions about alternatives for T2D and CKD management, including medication and lifestyle modification.

Consideration for implementation

Patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2 benefitted from SGLT2i therapy in RCTs. In subgroup analysis from the conducted trials, this held true for all patients, independent of age, sex, and race. Thus, this recommendation holds for patients of all ages, gender, and race. However, long-term follow up and further collection of real-world data are needed to confirm effectiveness and potential harms in specific patient populations.

Specifically, there is insufficient evidence evaluating 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.

Participants with eGFR as low as 30 ml/min/1.73 m^2 were included in the EMPA-REG, CANVAS, and CREDENCE trials,[219, 221, 223] and efficacy and safety in these studies were consistent across eGFR down to this threshold. Patients with G4 (GFR 15 to 29 ml/min/1.73 m^2) and G5 (ESKD, GFR <15 ml/min/1.73 m^2) were not included. Thus, SGLT2i initiation is

recommended for patients with eGFR ≥30 ml/min/1.73 m^2 but not those with eGFR <30 ml/min/1.73 m^2, for whom there is a lack of evidence of benefit and safety. In accordance with CREDENCE patients can continue SGLT2i if eGFR declines below 30 ml/min/1.73 m^2 until dialysis. More data are needed for initiation in eGFR < 30 ml/min/1.73 m^2.

The SGLT2i with proven kidney or cardiovascular benefit, their FDA approved-doses, and dose adjustments recommended in CKD are described in Table 9.

Rationale

For patients with CKD with eGFR ≥30 ml/min/1.73 m^2, the current KDIGO guideline recommends using SGLT2i together with metformin. The recommendation is strong due to the known kidney-protective and cardioprotective effects in patient with T2D and CKD as shown in high-quality trials, such as CANVAS, CREDENCE, DAPA-HF, DECLARE, and EMPA-REG. In the judgment of the Work Group, nearly all well-informed patients would choose to receive this treatment, rather than reduce their risk of diabetic ketoacidosis, mycotic infections, or foot complications.

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 ACC,[270] the joint statement by the ADA and the European Association of the Study of Diabetes (EASD),[271] and the joint statement by the European Society of Cardiology (ESC) and EASD.[272] The ADA guideline states that treatment with one of the SGLT2i with proven benefit is recommended for patients with T2D, who have either CKD, clinical heart failure, or ASCVD.[271]

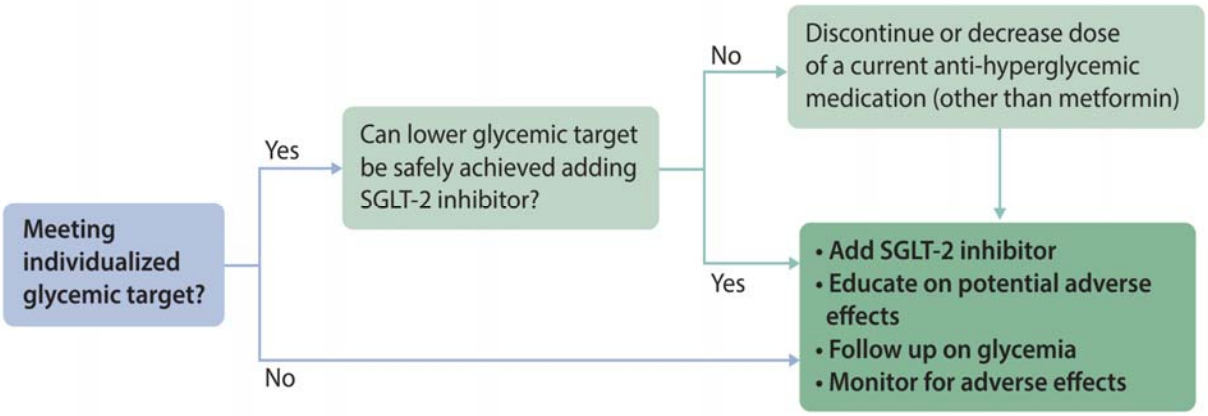
The 2019 ESC guideline provided a Class I recommendation to use SGLT2i for patients with T2D and ASCVD or at high/very high cardiovascular risk (which includes target organ damage such as CKD).[272] The difference between the ESC/EASD recommendation and the current KDIGO recommendation may stem from 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 study (ACR >300 mg/g and eGFR 30-90 ml/min/1.73 m^2) as CREDENCE was the only dedicated kidney outcome study, whereas benefit seen for patients with less albumin excretion comes from cardiovascular outcome trials with secondary kidney outcomes.

There is a lack of clarity across guidelines regarding initial therapy for patients not yet treated with an antihyperglycemic drug. Most guidelines suggest initial therapy with metformin, while the ESC guideline recommends initial therapy with an SGLT2i for patients with high CVD risk. The current KDIGO guideline recommends using both metformin and an SGLT2i for most patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2.

The efficacy and safety of SGLT2i has not been established in T1D. Use of SGLT2i 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 sotaglifozin for use in T1D as an adjunct to insulin.

Practice Point 4.2.1. A SGLT2i can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met and for patients who are meeting glycemic targets but can safely attain a lower target. (Figure 14)

Figure 14. Algorithm for initiation of SGLT2i therapy for patients with T2D, CKD, and eGFR ≥30 ml/min/1.73 m^2, who are already treated with anti-hyperglycemic medications



CKD = chronic kidney disease, DPP-4i = dipeptidyl peptidase inhibitor, eGFR = estimated glomerular filtration rate, GLP-1 RA = glucagon-like peptide-1 receptor agonist, SGLT2 = sodium–glucose cotransporter 2, T2D = type 2 diabetes.

For patients already treated with antihyperglycemic medications, the decision to initiate an SGLT2i needs to be made in the context of the existing medical regimen. The risk of hypoglycemia is low with SGLT2i monotherapy, as the drug-induced glycosuria decreases as blood glucose normalizes, but risk may be increased when used concomitantly with other medications that can cause hypoglycemia such as sulfonylureas or insulin. For patients not attaining glycemic targets, it is reasonable to add an SGLT2i to existing antihyperglycemic therapy, educate on potential adverse effects, and following up to ascertain changes in glycemic control and symptoms. For patients attaining glycemic targets, particularly those who are not experiencing hypoglycemia and those using only medications with low risk of hypoglycemia (e.g., metformin, GLP-1 RA, DPP4i, thiazolidinedione, acarbose), it may be possible to safely achieve a lower target with the addition of an SGLT2i.

Practice Point 4.2.2. For patients in which additional glucose lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.

The risk of hypoglycemia is low with SGLT2i, as the drug-induced glycosuria decreases as blood glucose normalizes, but risk may be increased when used concomitantly with other medications that can cause hypoglycemia such as sulfonylureas or insulin. If tighter glycemic control increases risk of hypoglycemia (e.g., more hypoglycemia due to insulin or sulfonylureas when overall glycemic control is improved), it is recommended that the dose of the other antihyperglycemic medication (excluding metformin which should be continued) is reduced or discontinued so that SGLT2i can be safely started. (Figure 14) This is particularly important when GFR is >45 to 60 ml/min/1.73 m^2.

Practice Point 4.2.3. Choice of SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

The table below shows current FDA approved doses which were primarily determined by the progressively less dramatic effect on blood glucose lowering at lower levels of eGFR. Since the SGLT2 inhibitors were indicated for glucose lowering, this seemed to justify lower doses at lower levels of eGFR. As the SGLT2 inhibitors are now indicated for organ protection independent glucose-lowering effect, the labels are expected to change, and have already been changed by FDA for canagliflozin and in Canada for empagliflozin to reflect the studies including patients with eGFR >30 ml/min/1.73 m^2.

Table 9. SGLT2i with established kidney and cardiovascular benefits and doses adjustments as approved by FDA (be aware of country-to-country variation)

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials
Dapagliflozin	5–10 mg once daily	No dose adjustment if eGFR ≥ 45 mL/min/1.73m² Not recommended with eGFR < 45 mL/min/1.73m² Contraindicated with eGFR < 30 mL/min/1.73m²
Empagliflozin	10–25 mg once daily	No dose adjustment if eGFR ≥ 45 mL/min/1.73m² Avoid use, discontinue with eGFR persistently < 45 mL/min/1.73m²
Canagliflozin	100–300 mg once daily	No dose adjustment if eGFR > 60 mL/min/1.73m² 100 mg daily if eGFR 30–59 mL/min/1.73m² Avoid initiation with eGFR < 30 mL/min/1.73m², discontinue dialysis

eGFR = estimated glomerular filtration rate, FDA = Food and Drug Administration, SGLT2 = sodium–glucose cotransporter 2

Practice Point 4.2.4. It is reasonable to withhold SGLT2i during times of prolonged fasting 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 Harms section of Recommendation 4.2.1. for more details]

Practice Point 4.2.5. If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i and advising patients about

symptoms of dehydration and low blood pressure, and follow up volume status after drug initiation.

SGLT2i cause an initial natriuresis with accompanying weight reduction. This may contribute to one of the benefits of SGLT2i, 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 with tenuous volume status. Despite this theoretical concern, clinical trials have shown that the incidence of AKI is decreased with SGLT2i, compared with placebo.[249] 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 for volume status.

Practice Point 4.2.6. A reversible decrease in eGFR with commencement of SGLT2i may occur and is generally not an indication to discontinue therapy.

The landmark RCTs demonstrated a reversible decrease in eGFR among those treated with SGLT2i.[273] 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 kidney death. Pooled results of the four large RCTs which published in kidney outcomes demonstrated that risk of AKI is significantly lower with SGLT2i,[249] so a modest (≤30%) initial drop in eGFR should not necessitate stopping the SGLT2i.

Practice Point 4.2.7. Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min/1.73 m^2, unless reversible changes in eGFR are precipitating uremic symptoms or other complications of CKD.

When a patient's eGFR falls below the minimum level suggested to initiate the agent, if an SGLT2i more appropriate to the new level of eGFR is available, a switch could be made to the more appropriate SGLT2i (Table 9). For example, for a patient treated with empagliflozin who has a sustained fall in eGFR to 40 ml/min/1.73 m^2 not attributable to the SGLT2i, it would be reasonable to replace empagliflozin with canagliflozin. This approach was taken in the CREDENCE trial[221] and is analogous to that taken for RAAS inhibitors.

Practice Point 4.2.8. SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients.

RESEARCH RECOMMENDATIONS

- Studies focused on long-term (>5 years) safety and efficacy of SGLT2i among patients with T2D and CKD are needed. We need continued longer safety follow-up data and post-marketing surveillance.
- Evidence to confirm clinical evidence of cardiovascular outcome benefit among patients with T2D and CKD but without established CVD/heart failure (i.e., more data in primary prevention population).
- Studies focused on cardio- and kidney-protective benefits of SGLT2i for patients with T1D are needed.
- Studies to establish whether there is safety and clinical benefit of SGLT2i for patients with T2D in CKD G4-G5.
- Studies to establish whether there is safety and clinical benefit of SGLT2i for patients with T2D in kidney transplant recipients who are at high risk of both graft loss and infection.
- Studies examining whether there is safety and efficacy of SGLT2i among individuals with a history of T2D and CKD, but who now have controlled HbA1c <6.5%.
- Studies examining the safety and benefit of SGLT2i for patients with CKD without proteinuria.
- Cost-effectiveness analysis of this strategy prioritizing SGLT2i among patients with T2D and CKD over other diabetes medications, factoring in cardiovascular and kidney benefits against the cost of medications and potential for adverse effects.
- Studies to further investigate whether the cardio- and kidney benefits are consistent across all SGLT2i ("class effect") or whether there are unique differences to specific SGLT2i agents.
- Studies to investigate whether a similar risk reduction would be seen if patients are under optimal blood pressure control and multifactorial treatment (i.e., How much of the kidney benefit in CREDENCE is explained by lower blood pressures?)
- Future work to address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake among low-resource setting.

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

Background

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the intestine after ingestion of glucose or other food nutrients and stimulates glucose-dependent release of insulin from the pancreatic islet cells. GLP-1 also slows gastric emptying and decreases appetite stimulation in the brain, facilitating weight loss. The incretin effect is reduced or absent in patients with T2D.

Long-acting GLP-1 receptor agonist (GLP-1 RA) medications, which stimulate this pathway, have been shown to significantly improve blood glucose and HbA1c control, confer weight loss, and reduce blood pressure. More importantly though, several GLP-1 RA agents have been shown to reduce MACE in patients with T2D with persistent HbA1c elevation >7.0%, who were at high cardiovascular risk.[274-277] Additionally, these same GLP-1 RA agents have been shown to have favorable kidney benefits with substantial reduction in albuminuria and likely preservation of eGFR.[274, 277, 278]

Recommendation 4.3.1. In patients with Type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin SGLT2i, or who are unable to use those medications, we recommend a long acting glucagon-like peptide-1 receptor agonist (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

GLP-1 RA and cardiovascular outcomes

There are currently six published large RCTs examining cardiovascular outcomes for injectable GLP-1 RA[274-280] and one trial of an oral GLP1-RA.[281] (Table 10) Of these, four studies (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER),[277] SUSTAIN-6,[276] HARMONY,[275] and REWIND[274]) have confirmed cardiovascular benefit of four injectable GLP-1 RA with significant reductions in MACE events for liraglutide, semaglutide, albiglutide, and dulaglutide, respectively. The other agents (lixisenatide, exenatide, and oral semaglutide) have been shown to have cardiovascular safety, but without significant cardiovascular risk reduction.

The LEADER trial (evaluating liraglutide) included 9,340 individuals with T2D and HbA1c ≥7% with high cardiovascular risk defined as established cardiovascular disease, CKD of Stage 3 or higher, age ≥60 years, or a major CVD risk factor.[277] Of note, LEADER also included 220 individuals with eGFR 15 to 30 ml/min/1.73 m^2. LEADER compared once-daily liraglutide compared to placebo and followed participants for a median of 3.8 years for primary MACE outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. There was a 13% reduction in MACE [HR 0.87 (95% CI 0.78, 0.97)] conferred by liraglutide.

In LEADER, the risk reduction for the primary composite MACE outcome was even greater among individuals with CKD G3a or greater severity (eGFR <60 ml/min/1.73 m^2) compared to those with eGFR ≥60 ml/min/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].[282] This benefit was seen across each separate cardiovascular outcome. Notably, liraglutide (compared to placebo) conferred an impressive 49% reduction for non-fatal stroke; with HR 0.51 (95% CI 0.33, 0.80) for eGFR <60 ml/min/1.73 m^2 versus HR 1.07 (95% CI 0.84, 1.37) for eGFR ≥60 ml/min/1.73 m^2. While subgroup analyses should be considered cautiously, these findings suggest that efficacy among individuals with CKD is at least as great as for those without CKD.

The SUSTAIN-6 trial (evaluating injectable semaglutide) enrolled 3,297 patients with T2D and HbA1c ≥7% with CVD, CKD Stage 3 or higher, or age ≥60 years with at least one major CVD risk factor.[276] 83% 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 eGFR <30 ml/min/1.73 m^2 versus ≥30 ml/min/1.73 m^2 (p-interaction = 0.98) and similar reduction for those with eGFR <60 ml/min/1.73 m^2 versus ≥60 ml/min/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%.[275] Of note, an eGFR <30 ml/min/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, MI, 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/1.73 m^2, ≥60 to 90 ml/min/1.73 m^2, and ≥90 ml/min/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%).[274] An eGFR <15 ml/min/1.73 m^2 was an exclusion criterion. REWIND enrolled a low proportion of patients with established CVD (31.5%); thus, it is largely a primary prevention trial. REWIND 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 non-fatal MI, non-fatal 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 and without previous CVD (p-interaction = 0.97).

In contrast, the ELIXA (lixisenatide)[280] and EXSCEL (exenatide)[279] trials did not show a cardiovascular benefit with GLP-1 RA, nor did they find increased harm, confirming cardiovascular safety. Differences in ELIXA and EXSCEL versus the more favorable results

seen in LEADER, SUSTAIN, HARMONY, and REWIND may be differences in GLP-1 RA molecular structures, half-lives, and formulations, study design differences, or patient populations studied. For example, ELIXA trial had a high discontinuation and drop-out rate.

Finally, the PIONEER 6 study investigated the cardiovascular safety of an oral GLP-1 RA (oral semaglutide).[281] PIONEEER 6 evaluated 3,183 patients with T2D and high cardiovascular risk, CKD, or age >50 with a major CVD risk factor. An eGFR <30 ml/min/1.73 m^2 was an exclusion criterion. Oral semaglutide was found to be not inferior to placebo for primary MACE outcome. Furthermore, there was no difference in the primary outcome for participants with eGFR <60 ml/min/1.73 m^2 versus ≥60 ml/min/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 eGFR <60 ml/min/1.73 m^2.

A 2019 meta-analysis of the seven trials of GLP-1 RA (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, and PIONEER 6), which together included a total of 56,004 participants, evaluated pooled cardiovascular and kidney outcome data in the general diabetes population, including patients with CKD.[283] Compared to placebo, GLP-1 RA treatment conferred a reduction in cardiovascular death [HR 0.88 (95% CI 0.81, 0.96)], stroke [HR 0.84 (95% CI 0.76, 0.93)], MI [HR 0.91 (95% CI 0.84, 1.00)], all-cause mortality [HR 0.88 (95% CI 0.83, 0.95)], and hospitalization for heart failure [HR 0.91 (95% CI 0.83, 0.99)]. Of note, this is the first time a signal of benefit for heart failure hospitalization has been demonstrated for the GLP-1 RA class of medications, although the effect was not as large of a reduction as what has been previously demonstrated for SGLT2i.

<u>GLP1RA and kidney outcomes</u>

The LEADER trial also examined the effects of liraglutide compared to placebo on a pre-specified secondary composite kidney outcome (new onset severely increased albuminuria, doubling of serum creatinine, ESKD, or kidney death).[284] Liraglutide conferred a significant 22% reduction in this composite kidney outcome [HR 0.78 (95% CI 0.67, 0.92)] which was primary driven 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 ESKD, and few kidney deaths occurred in the study.

In SUSTAIN-6, there was also a reduction in new or worsening nephropathy with semaglutide compared to placebo [HR 0.64 (95% CI 0.46, 0.88)].[276] This composite kidney outcome included 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.[285] There was a 15% reduction in the composite kidney

outcome defined as new severely increased albuminuria (ACR of >33.9 mg/mmol), 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. As usual, exploratory results should be interpreted cautiously and as hypothesis-generating. There were no serious adverse events for kidney disease in REWIND. Among the 9,901 participants, 22.2% had eGFR <60 ml/min/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 eGFR ≥60 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2 (p-interaction = 0.65), and similar benefit among subgroups defined by baseline albuminuria status and use of ACEi or ARB. Of note, the HbA1c lowering and blood pressure-lowering effects of dulaglutide explained 26% and 15%, respectively of the kidney benefits conferred by dulaglutide. Hence, not all of the benefit of GLP1-RA is explained by improved CKD risk factors.

Another important study that supports a potential kidney benefit and emphasizes safety of a GLP-1 RA for glycemic control in the CKD population was the AWARD-7 trial, which compared dulaglutide to insulin glargine among patients with moderate-to-severe CKD.[278] While glycemic indices were primary outcome of the trial, kidney outcomes (eGFR and ACR) were pre-specified secondary outcomes. AWARD-7 enrolled patients with CKD G3a to G4 (mean eGFR 38 ml/min/1.73 m^2) who were being treated with ACEi or ARB and found that dulaglutide conferred significantly less eGFR decline over 52 weeks (mean -3.3 ml/min/1.73 m^2 vs. -0.7 ml/min/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/1.73 m^2 vs. -0.7 ml/min/1.73 m^2 and -0.5 ml/min/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 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 moderate-to-severe CKD. As a result, dulaglutide has received FDA approval for glycemic control in T2D with eGFR as low as 15 ml/min/1.73 m^2.

As mentioned above, a 2019 meta-analysis was conducted of seven cardiovascular outcomes trials of GLP-1 RA (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, and PIONEER 6).[283] Compared to placebo, GLP-1 RA treatment reduce risk for a broad composite kidney outcome (development of new severely increased albuminuria, decline in eGFR, or rise in serum creatinine, progression to ESKD, or death from kidney cause) [HR

0.83 (95% CI 0.78, 0.89)] in the general diabetes population, including patients with CKD. In these study groups selected for cardiovascular risk, kidney endpoints were largely driven by reduction in albuminuria. Excluding severely increased albuminuria, the association of GLP-1 RA with kidney endpoints was not significant [HR 0.87 (0.73, 1.03)].[283]

One 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 outcome (as was done in the CREDENCE trial for canaglifozin[221]). A clinical trial of GLP-1 RA in patients with diabetes and CKD with a primary kidney disease outcome is needed. Notably, such data should be forthcoming with the on-going FLOW trial (NCT03819153) that will evaluate whether semaglutide among patients with T2D and eGFR 25 to 50 ml/min/1.73 m^2 or with severely increased albuminuria on a background of standard-of-care with ACEi or ARB therapy confers kidney benefit.

GLP-1 RA and cardiometabolic benefits

The favorable effects of GLP-1 RA on risk factors (i.e., reductions in glucose, blood pressure, and weight) may contribute to the favorable cardiovascular and CKD outcomes versus placebo or insulin therapy. GLP1-RA are more potent glucose-lowering agents compared to SGLT2i in the CKD population and also confer greater weight loss potential.

Harms

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

Side-effects of GLP-1 RA may preclude use of 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.[286] There also might be injection site reactions and increase in heart rate with this therapy, and GLP-1 RA should be avoided in patients at risk for thyroid C-cell tumors and with a history of acute pancreatitis.

Low eGFR dose adjustment is required for exenatide and lixisenatide. However, given that the ELIXA[280] and ESXCEL[279] trials did not prove any cardiovascular benefit with these agents, priority would be to use one of the other available GLP-1 RA which have shown CVD and CKD benefits (i.e., liraglutide, semaglutide, and dulaglutide). However, 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 to prevent end-organ damage (heart and kidney) as well as manage hyperglycemia. Initiation of GLP-1 RA must take into account other anti-hyperglycemic agents, especially those associated with hypoglycemia which may require changes to these medications. Of note, in the largest meta-analyses conducted to date with

seven GLP-1 RA trials including 56,004 participants, there was no increased risk noted of severe hypoglycemia, pancreatitis, or pancreatic cancer.[283]

While GLP-1 RA and SGLT2i reduce MACE to a similar degree, GLP1 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 eGFR ≥30 ml/min/1.73 m^2, SGLT2i are preferred over GLP-1 RA as initial anti-hyperglycemic and organ protective agent with metformin. 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 SGLT2i.

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 in patients with a history of acute pancreatitis.

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

Table 10. Cardiovascular and kidney outcome trials for GLP1RA

	ELIXA	LEADER	SUSTAIN	EXSCEL	HARMONY	REWIND	PIONEER 6	AWARD-7
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)	Dulaglutide
Total number of participants	6068	9340	3297	14,752	9463	9901	3183	577
N (%) with CVD	100%	81.3%	83%	73%	100%	31.5%	84.7%	
eGFR criteria for enrollment (mL/min per 1.73 m^2)	76	Most had eGFR ≥ 30, but did include 220 patients with eGFR 15 to 30			eGFR ≥ 30	eGFR ≥ 15	eGFR ≥ 30 (however 0.9% had eGFR < 30)	
Mean eGFR at enrollment (mL/min/1.73 m^2)		80	~75	76	79	76.9	74±21	38
N (%) with eGFR < 60 mL/min/1.73 m^2		20.7% with eGFR 30 to < 60 mL/ min/1.73m^2, 2.4% with eGFR < 30 mL/min/1.73m^2				22.2%	26.9%	100% CKD G3a–G4
ACR						7.9% with macroalbuminuria		44% with macroalbuminuria
Follow-up time	25 months	3.8 years	2.1 years	3.2 years	1.6 years	5.4 years	15.9 months	52 weeks
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	NA
CV outcome results	HR 1.02 (0.89, 1.17)	HR 0.87 (0.78, 0.97)	HR 0.74 (0.58, 0.95)	HR 0.91 (0.83, 1.00)	HR 0.78 (0.68, 0.90)	HR 0.88 (0.79, 0.99)	HR 0.79 (0.57, 1.11)	NA
Kidney outcome (secondary end points)		New-onset persistent macroalbuminuria, persistent doubling of the SCr level, ESKD, or death due to kidney disease	Persistent macroalbuminuria, persistent doubling of SCr, a CrCl of < 45 mL/min, or need for kidney replacement therapy			New macroalbuminuria ACR of > 33.9 mg/mmol, a sustained fall in eGFR of 30% from baseline, or use of kidney replacement therapy		
Kidney outcome results		HR 0.78 (0.67, 0.92)	HR 0.64 (0.46, 0.88)			HR 0.85 (0.77, 0.93) Similar for eGFR ≥ 60 vs. < 60 mL/min/1.73m^2, no albuminuria vs. albuminuria, no ACEi/ARB vs. ACEi/ARB		eGFR did not significantly decline (0.7 mL/min/1.73 m^2) with dulaglutide 1.5 mg or dulaglutide 0.75 mg, whereas eGFR decreased by –3.3 mL/min/1.73m^2 with insulin glargine

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II recptor blockade, CrCl = creatinine clearance, CV = cardiovascular, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease, GLP-1RA = glucagon-like peptide-1 receptor agonist, HR = hazard ratio, MI = myocardial infarction, NA = not available, SCr = serum creatinine; ACR = albumin-creatinine ratio

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,[274-277, 279-281] a meta-analysis of these seven RCTs combining efficacy data for cardiovascular and kidney outcomes,[283] and an updated Cochrane systematic review and meta-analysis[256] in patients with diabetes and CKD conducted by the ERT (Tables S20).[274, 275, 278, 279, 287-294] From this data, there is moderate of certainty the evidence that GLP-1 RA reduce MACE among patients with T2D. The certainty of the evidence was downgraded to moderate because of inconsistency of the data, with an I^2 = of 59%.

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. The updated Cochrane review identified fewer data for kidney composite outcomes in participants with CKD, with unclear benefits in participants with CKD G3a to G5 (Table S20).[274, 275, 278, 279, 287-294] There also has not been a designated trial published to date with primary endpoint of kidney outcomes, although the on-going FLOW trial (NCT03819153) should address whether GLP-1 RA can slow progression of CKD in T2D.

- *Study design:* there have now been multiple RCTs, with 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 pre-defined secondary outcomes or as 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.[283]

- *Risk of bias:* The risk of bias is low as the seven large RCTs studies demonstrated good allocation concealment, adequate blinding, with complete accounting for all patients and outcome events. In the aforementioned meta-analysis of seven RCTs of GLP-1 RA, the authors found that all trials were high-quality and met criteria for low risk of bias as assessed by the Cochrane tool.[283] However, in the updated Cochrane review, there was concern about incomplete outcome data because of attrition rates for the outcome all-cause mortality.

- *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), but no heterogeneity was observed for secondary outcomes, including kidney outcomes across baseline eGFR and baseline ACR groups.

- *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 studies conducted included large numbers of study participants with acceptable event rates, and therefore narrow confidence intervals.

- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. However, the majority of studies were commercially funded.

Values and preferences

The Work Group judged that all or nearly all well-informed patients with T2D and CKD who cannot take an SGLT2i because of tolerance or a contraindication would choose to receive a GLP-1 RA because of the cardiovascular benefits associated with this class of medications. Patients with history of ASCVD or at high risk for ASCVD who are in need of further glycemic management might be particularly inclined to choose a GLP1-RA. In contrast, patients who experience severe gastrointestinal side effects, 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

While some models have found the use of GLP-1 RA to be a cost-effective strategy among patients with T2D,[295, 296] these medications are frequently cost-prohibitive for many patients compared to other cheaper oral diabetes medications (notably sulfonylureas) which unfortunately do not have same level of evidence for cardiovascular and kidney benefits. In many cases, obtaining pre-authorizations from insurance companies for GLP-1 RA places undue burden on healthcare professionals and patients. Even with insurance coverage, many patients are still faced with significant co-payment.

Availability of drugs also vary between countries and regions. Thus, treatment decisions must take into account patient's preference, drug availability in local 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 afford them.

Consideration for implementation

For patients with T2D and CKD, after lifestyle measures, the Work Group recommends prioritizing metformin and SGLT2i as initial anti-glycemic medication in eligible patients. 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 anti-hyperglycemic agents given their established cardiovascular and potential kidney benefits

(Figure 11). This approach is consistent with the recommendations from other professional societies including the ACC,[270] the ADA,[271, 297] and the ESC/EASD.[272]

Patients with T2D and CKD benefitted 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 for all patients independent of age, gender, or race/ethnicity. Thus, this recommendation holds for all patients; however, long-term follow up and further 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 suspect different outcomes in this population. Conversely, there is less available safety data for CKD G5 or patients on kidney replacement therapy, so caution should be exercised in this group.[298] These medications may exacerbate gastrointestinal symptoms in peritoneal dialysis patients or those who are uremic or under-dialyzed, cachexia, and malnutrition. Still, GLP-1 RA are used in dialysis patients to avoid hypoglycemia.

Practice Point 4.3.1. The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

When the decision has been made to add a GLP1-RA, given that the ELIXA[280] (lixisenatide), ESXCEL (exenatide)[279] trials did not prove any cardiovascular benefit with these agents and that albiglutide is currently unavailable, priority would be to use one of the other GLP-1 RA which have shown cardiovascular and kidney benefit (i.e., liraglutide, semaglutide (injectable), and dulaglutide). Additionally, cardiovascular benefit has not been demonstrated for oral semaglutide, as PIONEER 6[281] was only powered for non-inferiority.

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

Practice Point 4.3.2. To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly. (Table 11)

Table 11. Dosing for available GLP-1 RA agents and dose modification for CKD

GLP-1 receptor agonist	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR > 15 mL/min/1.73m^2
Exenatide	10 µg twice daily	Use with CrCl > 30 mL/min
Exenatide Extended-Release	2 mg once weekly	Use with CrCl > 30 mL/min
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
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

CKD = chronic kidney disease, CrCl = creatinine clearance, eGFR = estimated glomerular filtration rate, ESKD = end-stage kidney disease, GLP-1RA = glucagon-like peptide-1 receptor agonist

Practice Point 4.3.3. GLP-1 RA should not be used in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors.

DPP-4 inhibitors reduce clearance of GLP-1 RA, and the two 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 GLP-1 RA instead.

Practice Point 4.3.4. The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when 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 to over classes of medications with less evidence supporting reduction of cardiovascular or kidney events (e.g., DPP-4 inhibitors, thiazolidinediones (TZDs), sulfonylureas, insulin, and acarbose). GLP-1 RA on their own do not cause hypoglycemia, but may increase the risk of hypoglycemia caused by sulfonylureas or insulin when used concurrently. Therefore, as with SGLT2i (Section 4.2), 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.

RESEARCH RECOMMENDATIONS

- Future studies should consider evaluating kidney outcomes as the primary outcome since prior studies have only examined kidney outcomes as only secondary or in exploratory analysis.
- Future evidence should confirm clinical evidence of cardiovascular outcome and kidney benefit of GLP-1 RA among patients with T2D in an exclusively CKD population since as prior studies have only examined CKD subgroups enrolled in the main trials.
- Future studies should focus on long-term (>5 years) safety and efficacy of GLP-1 RA among patients with T2D and CKD. We need continued longer safety follow-up data and post-marketing surveillance.
- Future studies should confirm the safety and clinical benefit of GLP-1 RAs for patients with T2D with severe CKD including those are dialysis, where there are limited data, as well as more data for CKD G4.
- Future studies should confirm the safety and clinical benefit of GLP-1 RAs for patients with T2D and kidney transplant.
- Future studies should examine what are the appropriate biomarkers to follow clinically to assess the clinical benefit of GLP-1 RA (i.e., HbA1c, body weight, blood pressure, albuminuria, etc.).
- Although REWIND provided encouraging results about the cardiovascular outcome benefit 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 its role as most studies have been secondary prevention.
- Future studies should focus on cardio- and kidney-protective benefits of GLP-1 RA, as well as safety, for use in patients with T1D.
- Future studies should examine whether there is safety and efficacy of GLP-1 RA among individuals with a history of T2D and CKD, but who now have controlled HbA1c <6.5%. For example, among CKD patients at high risk for ASCVD, is there a benefit for GLP-1 RA among individuals who are currently euglycemic?
- Future studies should report on cost-effectiveness of this strategy that prioritizes adding GLP-1 RA as third-line pharmacologic agent, after metformin and SGLT2i, among patients with T2D and CKD over other anti-glycemic medications, while factoring in cardiovascular and kidney benefits against the cost of medications and potential for adverse effects.
- Future studies should further investigate whether the cardio and kidney benefits are increased when GLP-1 RA are combined with SGLT2i.
- Future work should address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake among low-resource settings.

CHAPTER 5. APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Section 5.1. Self-management education programs

Recommendation 5.1.1. We recommend a structured self-management educational program be implemented for care of people with diabetes and CKD *(1C)*. (Table 12)

This 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 Care). The recommendation also places a relatively high value on the potential for such programs to enable 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.

Table 12. Key objectives of effective diabetes self-management education programs[299]

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 wellbeing, treatment satisfaction and quality of life

Key information

Balance of benefits and harms

Diabetes self-management education programs are guided by learning and behavior change theories and are tailored to a person's needs, and takes into account ethnic, cultural, literacy, cognitive and geographical factors.[299] The overall objectives of self-management programs are 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; to optimize individuals well-being, improve quality of life and to achieve treatment satisfaction.[299]

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 results in improvements in clinical (HbA1c, fasting glucose), body weight and psychosocial (diabetes self-knowledge, self-efficacy, self-management skills, patient satisfaction) outcomes.[300] The best approach is tailored to individual preferences and learning styles.[299]

Lifestyle management, including medical nutrition therapy, physical activity, weight loss, counselling 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, and physical activity, and increase self-efficacy. The best outcomes are achieved in those programs with a theory-based and structured curriculum and with contact time of over 10 hours with a patient-centered philosophy. While online programs may reinforce learning, there is little evidence to date they are effective when used alone.[301]

There is no expected or anticipated harm to patients if Diabetes Self-Management and Education Support (DSMES) 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 low cost benefit ratio, but otherwise there is usually not considered 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 are outlined as follows:

- Evidence-based
- Individualized to the needs of the person, including language and culture
- Has a structured theory-driven written curriculum with supporting materials
- Delivered by trained and competent individuals (educators) who are quality assured
- Delivered in group or individual settings
- Aligns with the local population needs
- Supports the person and their family 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 (i.e., travel, fasting)

- 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, quality of life
- Quality audited regularly

Quality of evidence

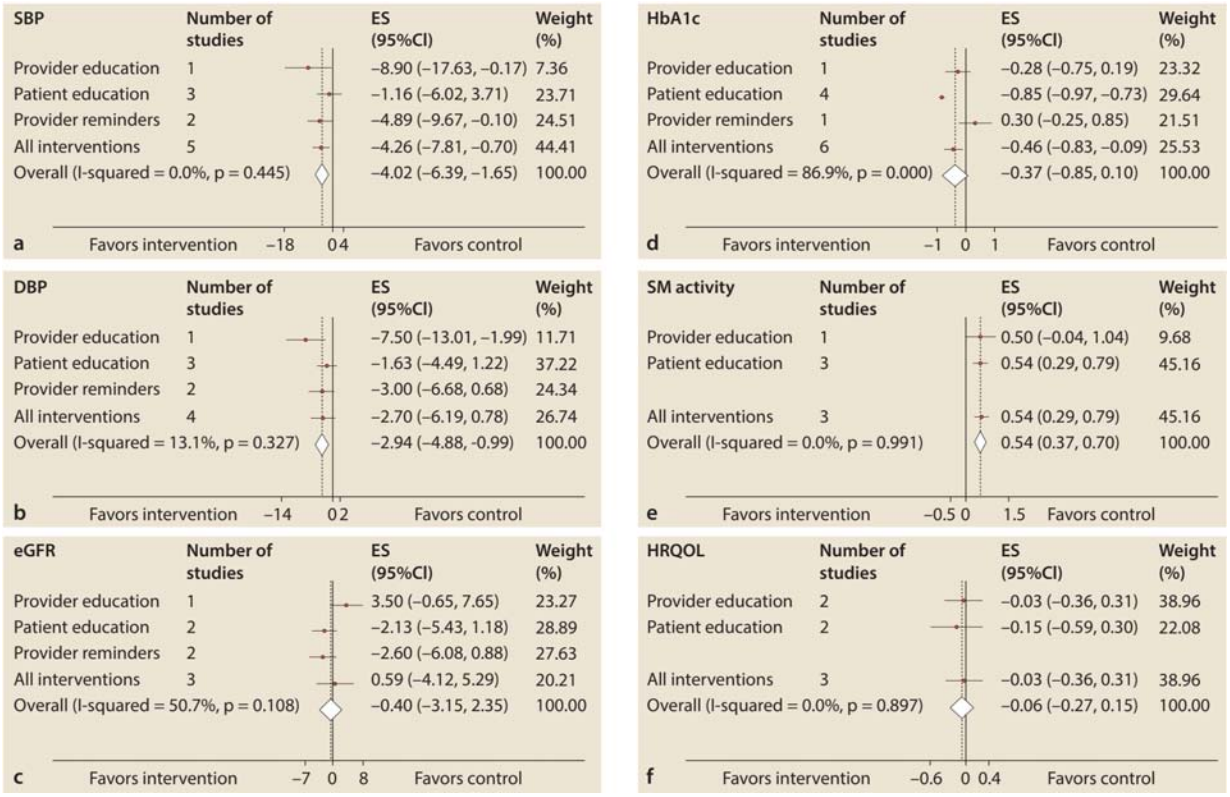
Overall the quality of the evidence was low because many critical and important outcomes were not reported, and surrogate outcomes exhibited low certainty of the evidence.

The evidence review included RCTs that focused on educational programs in patients with CKD and diabetes to prevent the progression of CKD, improve diabetic control, and improve quality of life. The review identified two RCTs that compared self-management education programs (specialist dietary advice) with multifactorial care in patients with CKD and diabetes (Table S21).[302-304] Only surrogate outcomes were reported and the certainty of the evidence was rated low due to very serious risk of bias (lack of blinding of outcome assessors, high lost to follow-up). Additionally, the evidence review identified one RCT that compared self-management education programs plus routine treatment with routine treatment alone (Table S22).[304, 305] This study exhibited low certainty of the evidence for the self-efficacy because of study limitations due to 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[306] was rated as a high-quality review according to systematic review critical appraisal tool AMSTAR 2.[307] The systematic review and meta-analysis of eight studies (Table S23) identified moderate certainty of the evidence for self-management activation and medication adherence outcomes (Figure 15 and Figure 16). The certainty 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.

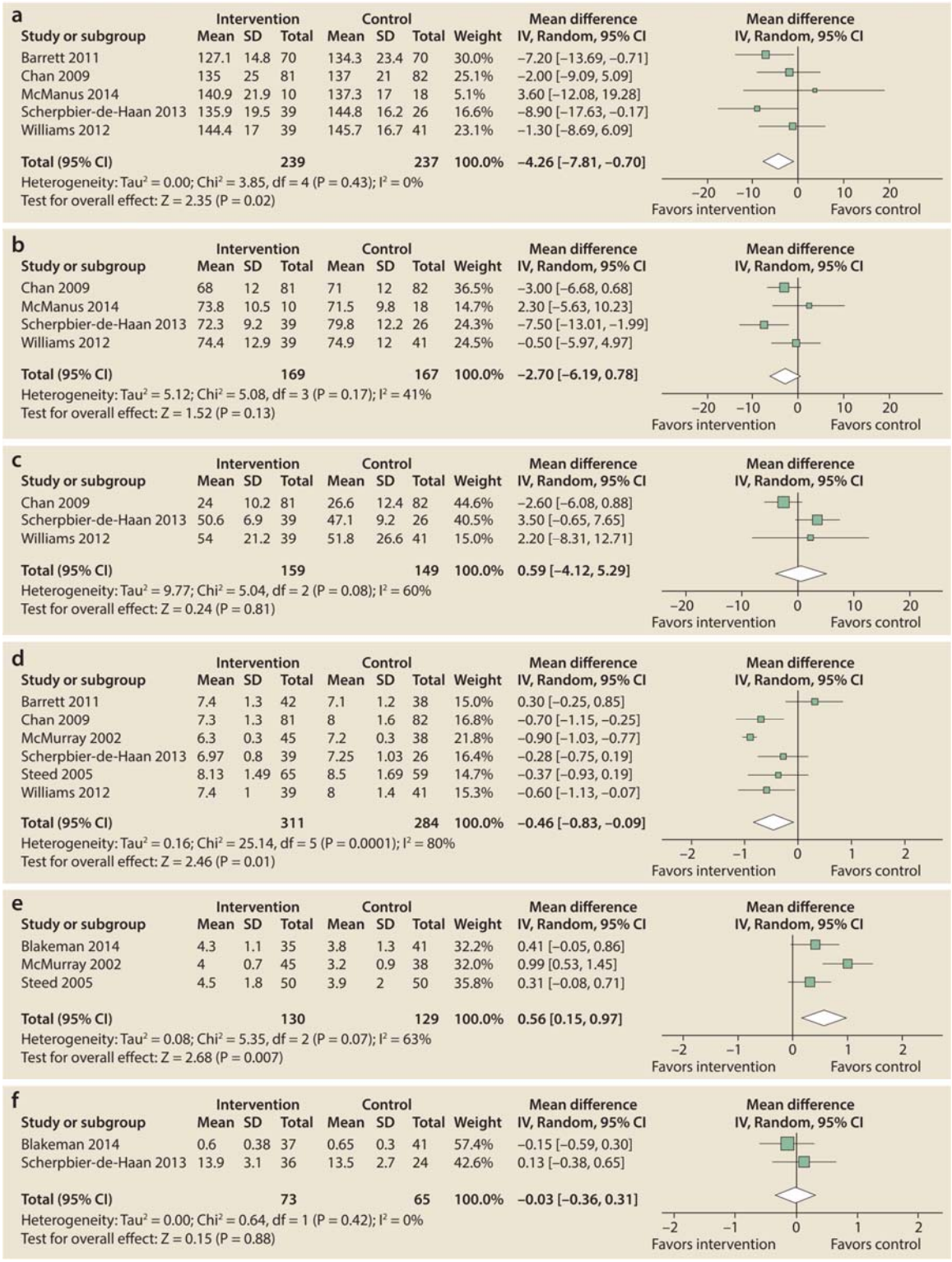
Additionally, other studies on self-management support in patients with CKD identified by the Work Group were observational studies and exhibit bias by design[308] or a small RCT[309] with various study limitations and hence the quality of the evidence was low.

Figure 15. Meta-analysis showing effect of different intervention components on a) systolic blood pressure, b) diastolic blood pressure, c) eGFR, d) HbA1c (%), e) self-management activity, and f) health-related quality of life[306]



BP = blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin

Figure 16. Forest plots showing outcomes for people with diabetes and CKD undergoing self-management education programs for a) systolic BP, b) diastolic BP, c) eGFR, d) HbA1c, e) self-management activities and f) health-related quality of life[306]



BP = blood pressure, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin

Values and preferences

The Work Group judged that diverse self-management education programs allow for informed decision-making and support. These would include face-to-face, group based, or digital self-management programs. In addition, the Work Group judged that patients would value that the programs be available and delivered in ethnic languages appropriate for the health care setting and taking into account the values, preferences, and the 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 is at 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 Care). The recommendation also places a relatively high value on the potential for such programs to enable 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 eight RCTs concluded that the reduction of clinical risk factors in self-management education programs are likely to be cost effective in the long-term. Another review of 22 studies suggested that self-management education programs are cost-effective or superior to usual care. The review also found that tele-medicine methods of delivering programs were potentially not cost effective. 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 cost savings, cost-effectiveness, reduced cost, or positive investment returns.

Considerations for implementation

Health care 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 at different stages of CKD and in people of different ethnic minority groups. Health care organizations need to be aware of these limitations and consider developing and evaluating programs that are tailored for their local populations. A number of definitions have been proposed to define self-management education program. The ADA defines diabetes self-management education as the ongoing process of facilitation knowledge, skills, and abilities necessary for diabetes self-care, and incorporates a person-centered approach and shared decision making.[186] NICE defines self-management education that constitutes of an evidence-based structured curriculum defining specific aims and objectives delivered by trained educators.[299] NICE also recommends that the programs are quality assured

and audited against consistent criteria by independent assessors.[311, 312] NICE recommends that a multidisciplinary team that includes at least one trained or accredited health-care practitioner, for example, a diabetes specialist nurse or dietitian, should 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 should be offered to people with diabetes at diagnosis with ongoing maintenance sessions.[312]

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, or via telemedicine, and can be delivered by different members of health-care teams.

Practice Point 5.1.1. Healthcare systems should consider implementing a structured program providing education on self-management 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 implementation of self-management 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 health-care teams depending on the availability in the health care setting.

RESEARCH RECOMMENDATIONS

- There is lack of specific self-management education programs for people with CKD, with dedicated effectiveness and cost-effectiveness. Future studies are needed to determine the effectiveness of these programs in multi-ethnic populations.
- Most evaluations of programs are short term and future studies should include evaluations of longer-term self-management of programs.
- Novel methods of delivering the self-management programs, including those delivered using technologies and one-on-one and group-based programs, should be pursued and evaluated.
- There is a lack of uptake of self-management programs even when available in a universal health-covered system such as the UK.[313, 314] Hence, further research should address methods of engagement and longer-term retention within programs.

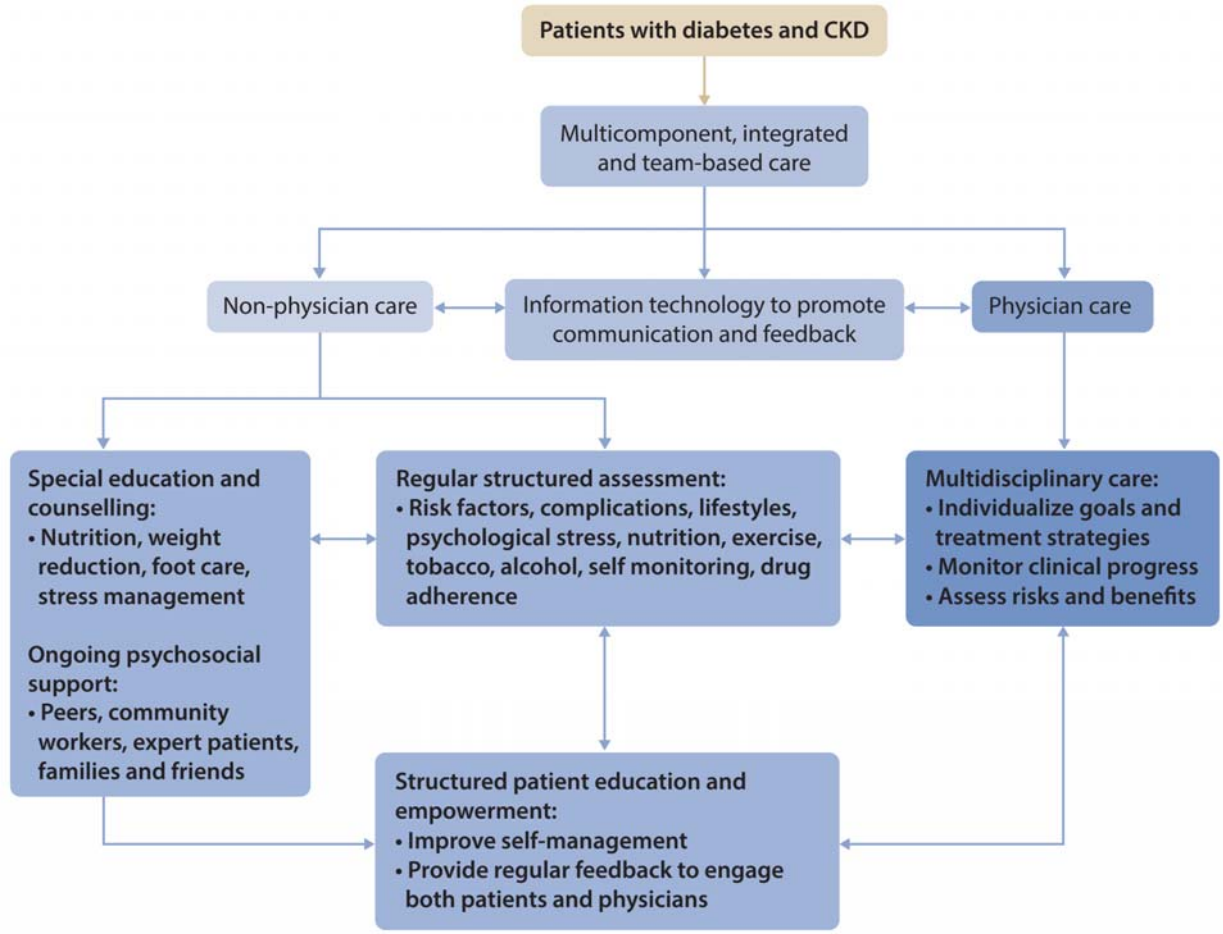
- Future evaluations of self-management programs should include assessment of duration, frequency of contacts, methods of delivery and content.
- Many minority ethnic groups have higher prevalence of diabetes and its associated complications. (e.g., migrant south Asian and Hispanic populations in the US) However, self-management education programs are often not tailored to suit minority populations.[299] However, culturally adapted programs may be effective especially if delivered with community support.[299] As such what are the key elements of a successful program that targets specific ethnic or minority population?

Section 5.2. Team-based integrated care

Recommendation 5.2.1. We suggest that policy-makers and institutional decision-makers should 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 (Figure 18) to improve outcomes, self-management, and patient-provider communication in patients with diabetes and CKD. 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 CKD and diabetes specifically.

Figure 17. A schematic diagram showing the use of physician and non-physician 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[271, 315-317]



CKD = chronic kidney disease

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 non-adherence with poor outcomes.[318-321] 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 (HCPs) and silent nature of risk factors and complications, there is a strong rationale to leverage on the complementary knowledge, skills, and experiences of physician and non-physician personnel; and 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.[316, 322]

Systematic reviews and meta-analyses support the benefits of multicomponent integrated care targeted at systems, patients, and care providers on reducing multiple cardiometabolic risk factors in T2D.[299, 323, 324] In a meta-analysis of 181 trials of various quality improvement strategies, patient education with self-management, task shifting and use of technology or non-physician personnel to promote patient-HCP communication have the largest effect size especially in low-resource settings. In 12 of these trials, hypoglycemia was a study outcome with nine trials indicating no between-group difference; two trials showed a reduction in hypoglycemia with intervention, and one trial, increased non-severe hypoglycemic events with intervention, albeit the rate was very low with no severe hypoglycemia.[323]

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 specialists' dietary advice with multifactorial care versus standard care (Table S24) exhibited moderate certainty of the evidence for critical outcomes including ESKD and HbA1c.[302] Trials that compared the addition of exercise advice and supervision,[325] exercise and diet.[325] or self-monitoring and medicine reviewing, and educational DVD (digital video disc) and follow-up calls[326] to standard care did not report on critical and important outcomes stipulated in this guideline.

A published systematic review (Table S25) that compared multicomponent integrated care lasting for at least 12 months duration with standard care in patients with diabetes exhibited moderate quality of the evidence.[323] The quality of the evidence was rated as moderate because of indirectness, as the review population (patients with diabetes) was different to the population of interest (patients with CKD and diabetes) in this population. However, some of the studies included in this review recruited included patients with CKD with ESKD as a study outcome measure.[327]

Values and preferences

In the judgment of the Work Group, health care providers need an optimal work environment and support system with appropriate infrastructures, facilities, and tools[328] to assess clinical needs and individualize care plans in order to bring out the best of clinical expertise and medical technologies. Apart from medical care, patients with diabetes with or without CKD may need advice, every now and then, from allied healthcare professionals such as dietitians, physical trainers, social workers, psychologists, or pharmacists on how to cope with the condition on a daily basis.[329] In some patients with T2D, especially those with social

disparity or emotional distress, psychosocial support from peers[330] and community healthcare workers[331] can also improve metabolic control, 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 which can be achieved only through team-based management. This care model may incur upfront investment needed to build capacity, re-train/re-deploy staff, re-engineer workflow and intensify ambulatory care including use of medications, which may lead to opportunity costs for intervention of other diseases. Over-treatment, 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 and high costs of cardiovascular-kidney complications, notably ESKD,[332] and the proven benefits of control of cardiometabolic and lifestyle risk factors on these outcomes,[2, 316, 333] the Work Group judged that this upfront investment is likely to be translated to long term benefits. .

Resources and other costs

In a two-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 over 50% reduced risk of cardiovascular-kidney events and all-cause death than those with suboptimal control.[327] In an RCT lasting for 7.8 years, high risk patients with T2D and moderately increased albuminuria who received team-based multifactorial care had 50% reduced risk of cardiovascular events compared to usual care.[4] These benefits were translated to reduced hospitalization rates and gain of 7.9 years of life after 20 years.[3, 334] Both of these team-based care models in patients with T2D and CKD focusing on treatment to multiple targets and self-management were found to be cost-effective and cost-saving, if implemented in the primary care setting.[335, 336]

Considerations for implementation

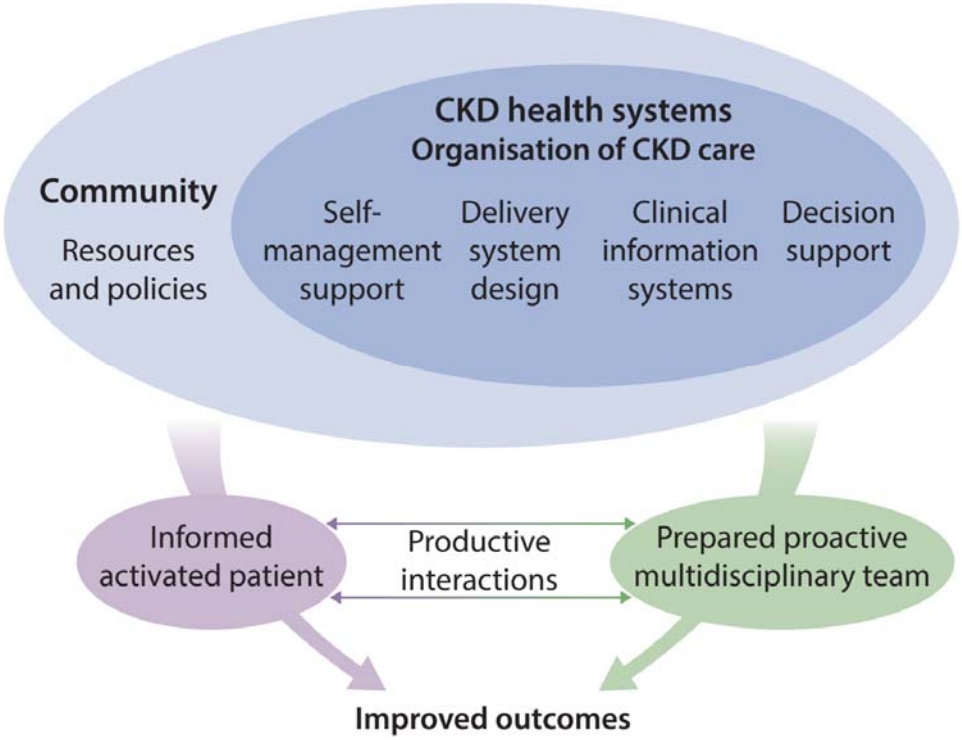
This recommendation recognizes potential resource constraints and insufficient capacity in delivering team-based care especially in some low- and middle-income countries. However, it is also these countries that often have the least resources to provide expensive care for advanced disease, making prevention 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 calls upon policymakers, planners and payers to build capacity, strengthen the system, and reward preventive care[337] to enable the delivery of evidence-based and value-added care for better outcomes.[271]

Rationale

Patients with diabetes and CKD have eight-fold higher risk of cardiovascular and all-cause mortality compared to those without diabetes and CKD.[338] Control of blood glucose, blood pressure and blood cholesterol as well as use of renin-angiotensin system inhibitors and statins have been shown to reduce the risk of cardiovascular-kidney disease.[320] However, in real-world practice, there are considerable care gaps in low, middle,[339] and high income countries.[340] 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.[316, 319] While 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.[299]

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.[322] (Figure 18) The concept of chronic care model focusing on team management, data collection and care integration shares analogy with the protocol-driven care in clinical trial settings where care coordination, treatment adherence and monitoring by non-physician staff is 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.[341, 342] 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 policy-makers would choose to adopt such models of care for this population, providing that resources were potentially available.

Figure 18. The chronic care model emphasizes the additive benefits of different components at the system, policies, providers and patient levels in improving clinical outcomes[323]



CKD = chronic kidney disease

Despite the potential value of these chronic care models, there are major implementation gaps due to factors pertinent to patients (e.g., motivation, adherence, support), systems (e.g., information, infrastructure, capacity), and HCPs (e.g., knowledge, skills, incentives). The relative importance of these factors is often context-specific and may vary between countries and within countries, as well as over time, depending on socioeconomic development and healthcare provision (single or multiple care providers, public, private or subsidized) or payment (social or private insurance) policies.

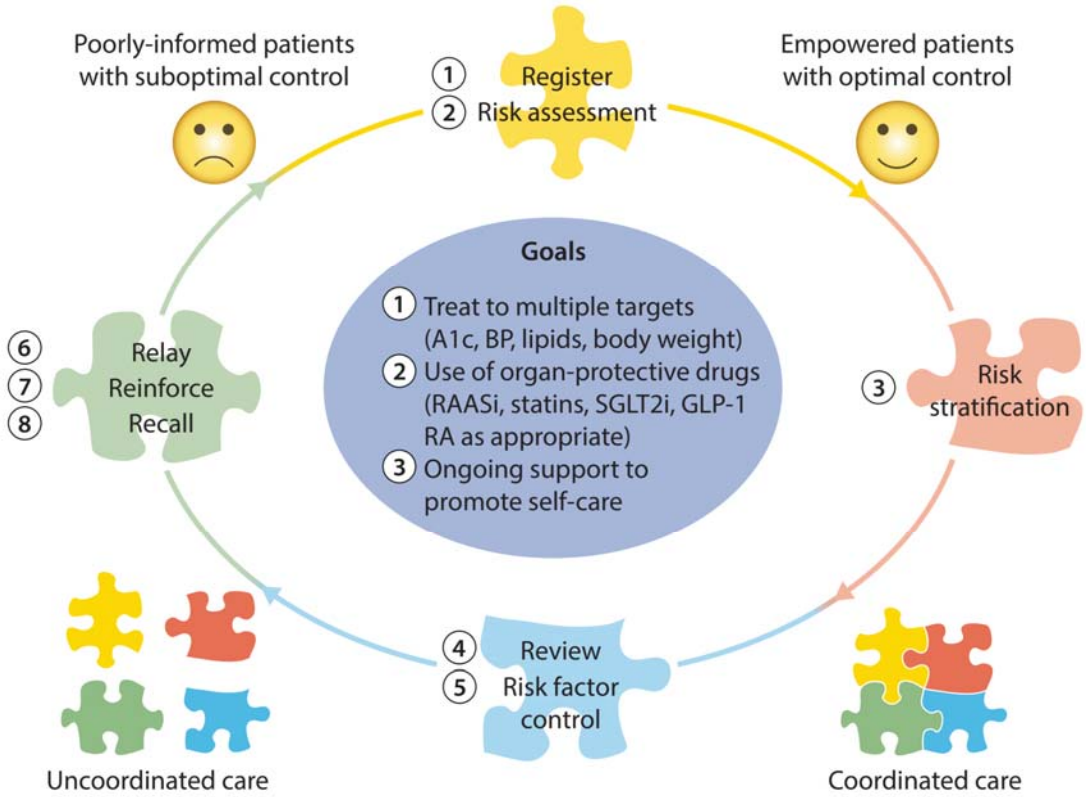
Practice Point 5.2.1. Team-based integrated care, supported by decision-makers, should be delivered by physicians and non-physician personnel (e.g., nurses, healthcare assistants, community workers, peer supporters). (Figure 19)

Decision makers allocate or redistribute resources, supported by appropriate policies, to facilitate the formation of a multidisciplinary team including physicians and non-physician personnel to deliver structured care in order to stratify risk, identify needs, individualize targets and treatment strategies. Within team-based structured care, practitioners should define care processes and re-engineer workflow, supported by information system with decision support, to deliver team-based structured care which consisted of the following:

a) establish a register by performing comprehensive risk assessment including blood/urine and eye/feet examination every 12-18 months as recommended by practice guidelines
b) assess cardiometabolic risk factors (e.g., blood pressure, glycated hemoglobin, body weight) every 2-3 months
c) assess kidney function (e.g., estimated glomerular filtration rate and ACR) every 6-12 months
d) review treatment targets and use of organ-protective medications (e.g., statins, RAASi, SGLT2i, GLP-1 RA as appropriate) at each visit
e) reinforce self-management (e.g., self-monitoring of blood pressure, blood glucose, body weight) and identify special needs at each visit
f) provide counselling on diet, exercise and self-monitoring with ongoing support and recall defaulters of clinic visit

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

Figure 19. Team-based integrated care delivered by physicians and non-physician personnel supported by decision- makers



HbA1c = glycated hemoglobin, BP = blood pressure, GLP-1 RA = glucagon-like peptide-1 receptor agonist, RAASi = renin-angiotensin-aldosterone system inhibitor, SGLT2i = sodium-glucose cotransporter 2 inhibitor.

RESEARCH RECOMMENDATIONS

- 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

To develop evidence-based clinical practice guidelines for the prevention of progression, monitoring and treatment of patients with diabetes and CKD. The guideline development methods are described below.

OVERVIEW OF THE PROCESS

These guidelines adhered to international best practice for guideline development.[343, 344] These guidelines have been conducted and reported in accordance with the AGREE II reporting checklist.[345] The processes undertaken for the development of the *KDIGO Clinical Practice Guideline on Diabetes Management in CKD* are described below.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Finalizing guideline development methodology
- Defining scope and topics of the guideline
- Formulating clinical questions – identifying the Population, Intervention, Comparator, Outcome, Methods (PICOM)
- Selecting topics for systematic evidence review and linking to existing Cochrane Kidney and Transplant systematic reviews
- Developing and implementing literature search strategies
- Selecting studies according to pre-defined inclusion criteria
- Data extraction and critical appraisal of the literature
- Evidence synthesis and meta-analysis
- Grading the quality of the evidence for each outcome across studies
- Grading the strength of the recommendation, based on the quality of the evidence, and other considerations
- Finalizing guideline recommendations and supporting rationales
- Public review in December 2019
- Guideline update.
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult nephrology, endocrinology, dietetics, epidemiology and public health, as well as patients. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of adult and pediatric nephrologists, and methodologists with expertise in evidence synthesis, and guideline development. 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 recommendations. The Work Group was responsible for writing the recommendations and underlying rationale, as well as grading the strength of the recommendation.

The KDIGO Co-Chairs, KDIGO Methods Chair, Work Group Co-Chairs, and the ERT met for a one-day meeting in Chicago in April 2018 to discuss and finalize the guideline development process and draft guideline topics with appropriate clinical questions to underpin systematic evidence review. The draft guideline topics and review topics were finalized with feedback from the Work Group.

Defining scope and topics and formulating key clinical questions

The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the *KDIGO Controversies Conference on the Management of Patients with Diabetes and* CKD.[320] Logical frameworks were developed to present a visual representation of the clinical question and facilitate discussion about the scope of the guideline. The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. However, for questions of critical importance, observational study data or systematic reviews of the general diabetes population were included. Clinical questions adhered to the Population, Intervention, Comparator, Outcome (a list of critical and important outcomes (Table 13)), and Method (PICOM) format. The Work Group and the ERT further refined the clinical questions to finalize inclusion and exclusion criteria to guide literature searching and data extraction. 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 with any Cochrane Kidney and Transplant systematic reviews, de-novo systematic reviews were undertaken. Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in the Table 14. All evidence reviews were conducted in accordance to the Cochrane Handbook,[346] and guideline development adhered to the standards of GRADE (Grades of Recommendation, Assessment, Development and Evaluation).[347]

Table 13. Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Cardiovascular mortality • ESKD • 3-point and 4-point major cardiovascular events • Individual cardiovascular events (myocardial infarction, stroke, heart failure) • Doubling serum creatinine

	• Hypoglycemia requiring 3rd party assistance • HbA1c
Important outcomes	• Albuminuria progression (onset of albuminuria, micro to macroalbuminuria)
Non-important outcomes	• eGFR/creatinine clearance

Table 14. Clinical questions and systematic review topics in PICOM format

Guideline chapter	Comprehensive care in CKD and diabetes
Clinical question	Do RAAS inhibitors improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) 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: hyperkalemia, acute kidney injury
Study design	RCTs
Cochrane systematic review	Strippoli GFM, 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.
Summary of findings tables	Table S4-S5, Table S26, Table S32-S33
Clinical question	Does dual RAAS inhibition compared to mono RAAS inhibition improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Intervention	Dual RAAS inhibition (ACEi and ARB)
Comparator	Mono RAAS inhibition (ACEi or ARB)
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: hyperkalemia, acute kidney injury
Study design	RCTs
Cochrane systematic review	Strippoli GFM, 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.
Summary of findings tables	Table S27
Clinical question	Does the addition of medication blocking the action of aldosterone on RAAS compared to standard of care or RAAS

	inhibition alone improve clinically important outcomes and reduce clinically relevant harms in patients with CKD and diabetes
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Intervention	Aldosterone antagonists or direct renin inhibitors
Comparator	Standard of care or RAAS inhibition
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: hyperkalemia, acute kidney injury
Study design	RCTs
Cochrane systematic reviews	Andad V, et al. Direct renin inhibitors for preventing the progression of diabetic kidney disease (Protocol). Cochrane Database Syst Rev. 2013:9; CD010724 Bolignano D, et al. Aldosterone antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2014:CD007004
Summary of findings tables	Table S28-S31
Clinical question	In patients with CKD (stage 1-5 CKD, dialysis-dependent, kidney transplant recipients) 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 (stage 1-5 CKD, dialysis-dependent) 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, acute kidney injury
Study design	RCTs
Cochrane systematic review	Natale P, et al. Potassium binders for chronic hyperkalemia in people with chronic kidney disease. Cochrane Database Syst Rev. 2018:CD013165
Summary of findings tables	Table S34-S37

Clinical question	Do antiplatelet therapies improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD (stage 1-5 CKD, dialysis-dependent, kidney transplant recipients) and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	Antiplatelet therapy
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: quality of life, fatigue, blood pressure
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	Table S38-S39
Clinical question	Does smoking cessation versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	Smoking cessation interventions
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: quality of life, fatigue, blood pressure, body weight, body mass index
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	Table S6
Clinical question	Does bariatric surgery versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in

	patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	Bariatric surgery
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: quality of life, fatigue, blood pressure, body weight, body mass index
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	No studies
Clinical question	In patients with diabetes and early CKD, does pharmaceutical weight loss therapies compared to placebo, no treatment or standard care improve weight loss or body weight outcomes.
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) 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: quality of life, fatigue, blood pressure, body weight, body mass index
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	Table S20

Guideline topic	Glycemic monitoring and targets in patients with diabetes and CKD
Clinical question	In adults with CKD and diabetes, what is the accuracy of HbA1c in diagnosing diabetes compared with frequently measured blood.
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Index test	HbA1c
Reference standard	Blood glucose (continuous glucose monitoring, fasting blood glucose, or multiple capillary blood glucose measurements)
Outcomes	Sensitivity and specificity
Study design	Diagnostic test accuracy reviews
Summary of findings tables	No relevant studies
Clinical question	In adults with CKD and diabetes, compared to HbA1c do alternative biomarkers improve clinically relevant outcomes and decrease clinically relevant harms?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Intervention	Alternative biomarkers (glycated albumin, fructosamine, carbamylated albumin)
Comparator	HbA1c or blood glucose monitoring
Outcomes	All-cause mortality, ESKD, CKD progression – doubling serum creatinine, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	No relevant studies
Clinical question	In adults with CKD and diabetes, what is the equivalency of alternative biomarkers with HbA1c to diagnose diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Index test	Alternative biomarkers (glycated albumin, fructosamine, carbamylated albumin)

Reference standard	HbA1c and glucose monitoring
Outcomes	Sensitivity and specificity
Study design	Diagnostic test accuracy reviews
Summary of findings tables	No relevant studies
Clinical question	In adults with CKD and diabetes, compared to HbA1c how well correlated are alternative biomarkers?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Index test	Alternative biomarkers (glycated albumin, fructosamine, carbamylated albumin)
Reference standard	Hba1c
Outcomes	Correlation co-efficient
Study design	Observational studies
Cochrane systematic review	None relevant
Summary of findings tables	Table S10
Clinical question	In adults with CKD and diabetes, compared to HbA1c does blood glucose monitoring (CGM, SMBG) improve clinically relevant outcomes and decrease harms?
Population	Adults with CKD (stage 1-5, dialysis-dependent) and diabetes (T1D and T2D)
Intervention	Glucose monitoring (CGM, SMBG)
Comparator	HbA1c
Outcomes	All-cause mortality, ESKD, CKD progression – doubling serum creatinine, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCTs
Cochrane systematic review	None relevant
Summary of findings tables	No relevant studies

Clinical question	In adults with CKD and diabetes, compared to HbA1c and blood glucose how well correlated are blood glucose monitors?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent) and diabetes (T1D and T2D)
Index test	Glucose monitoring (CGM, SMBG)
Reference standard	HbA1c
Outcomes	Correlation co-efficient
Study design	Observational studies
Cochrane systematic review	None relevant
Summary of findings tables	Table S11
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 CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, transplant recipients) 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	RCTs
Cochrane systematic review	Ruospo M, et al. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev. 2017:CD010137
Summary of findings tables	Table S7-9

Guideline chapter	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 CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) 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: quality of life, fatigue, blood pressure, body weight, body mass index
Study design	RCTs
Cochrane systematic review	Heiwe S and Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database of Systematic reviews. 2011; CD003236
Summary of findings tables	Table S17-18
Clinical question	Do dietary interventions activity versus usual diet improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) 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: quality of life, fatigue, blood pressure, body weight, body mass index
Study design	RCTs
Cochrane systematic reviews	McMahon EJ, et al. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2015:2; CD010070 Palmer SC, et al. Dietary interventions for adults with chronic kidney disease. Cochrane Database Syst Rev.

	2017;4:CD011998.
Summary of findings tables	Table S11-16, S40-44
Clinical question	Compared to usual diet does a high protein diet result in long-term harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	High protein diet
Comparator	Usual diet
Outcomes	Critical and important harms listed in Table 1
Study design	Systematic reviews
Summary of findings tables	No relevant systematic reviews
Guideline topic	Antihyperglycemic therapies in patients with diabetes and CKD
Clinical question	In patients with CKD and T2D, what are the effects of glucose lower medication on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) and diabetes (T1D and T2D)
Intervention	Older therapies - Metformin, sulfonylureas, or thiazolidinediones More recent therapies - alpha-glucosidase inhibitors, SGLT2i, GLP-1 RA, DPP-4 inhibitors
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes for GLP-1RA: body weight, BMI Long-term harms: hypoglycemia, lactic acidosis, amputation, bone fractures
Study design	RCTs Long-term harms – Systematic review of observational studies
Cochrane systematic reviews	Lo C, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. Cochrane Database Syst Rev. 2018:CD011798

	Lo C, et al. Glucose lowering agents for pre-existing and new onset diabetes in kidney transplant recipients. Cochrane Database Syst Rev. 2017:CD009966
Summary of findings tables	Table S19 - S20, S45-68
Guideline topic	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 CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) 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: quality of life and fatigue
Study design	RCTs
Cochrane systematic review	Li T, et al. Education programs for people with diabetic kidney disease. 2011:CD007374
Summary of findings tables	Table S21 - S23
Clinical question	What are the most effective health care delivery programs to improve clinically relevant outcomes and reduce clinically relevant harms in patients with CKD and diabetes?
Population	Adults with CKD (stage 1-5 CKD, dialysis-dependent, and kidney transplant recipients) 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: quality of life and fatigue
Study design	RCTs

Cochrane systematic reviews	None relevant
Summary of findings tables	Table S24 - S25, S69-70
Clinical question	What is the cost-effectiveness of multidisciplinary, team-based models of care in management of patients with diabetes?
Population	General diabetes population, and diabetes and CKD population
Intervention	Multidisciplinary or teams-based models of care
Comparator	Standard of care
Outcomes	Cost-effectiveness
Study design	Systematic reviews of cost-effectiveness studies
Summary of findings tables	No relevant reviews identified

Literature searches and article selection

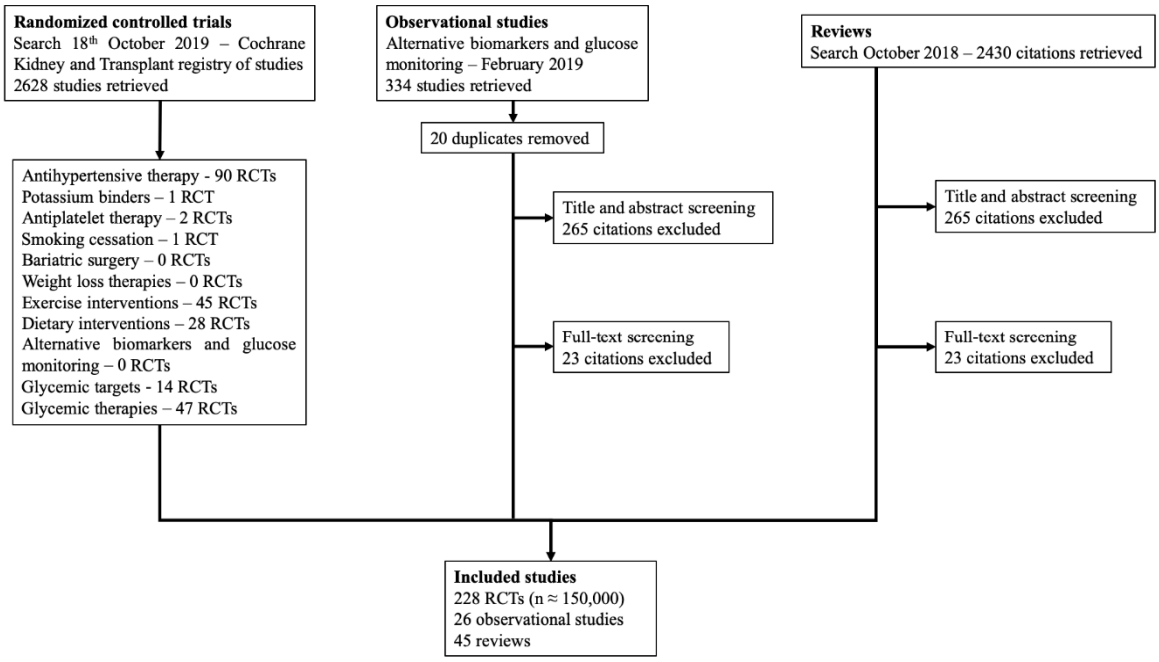
Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of Cochrane Central Register of 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 International Clinical Trials Register search portal.

For review topics that matched to 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 searched for clinical questions that only included RCTs and not linked to any an existing Cochrane systematic review. For clinical questions that included other study types, for example, diagnostic test accuracy studies, observational studies or systematic reviews on non-CKD populations, the medical literature databases MEDLINE and Embase were searched. The search strategies are provided in Supplementary Appendix Table S1.

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

A total of 5,392 citations were screened. Of these, 228 RCTs, 26 observational studies, and 45 reviews were included in the evidence review (Figure 20).

Figure 20. Search yield and study flow diagram



Data extraction

Data extraction was performed independently by two members of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner was included. The ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies

The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, The Cochrane Risk of Bias tool[348] 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 a risk of bias?

For some topics where there were no RCTs in the CKD population, the ERT conducted reviews of existing systematic reviews. AMSTAR 2[307] was used to critically appraise systematic reviews. For systematic reviews of diagnostic test accuracy studies, the QUADAS-2 tool[349] was used to assess study limitations. Additionally, for reviews that examined the correlation of alternative biomarkers and glucose monitoring with measures of blood glucose, an adapted QUADAS-2 tool[349] was used to assess the risk of bias. All critical appraisal was conducted independently by two 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

Measures of treatment effect - Dichotomous outcomes (all-cause mortality, cardiovascular mortality, ESKD, cardiovascular events (MACE, and individual events - myocardial infarction, stroke, heart failure), doubling serum creatinine, microalbuminuria to macroalbuminuria progression, hypoglycemia requiring 3rd party assistance) results were expressed as risk (RR) with 95% CI. For time-to-event data (MACE), HRs with 95% CI were reported, when continuous scales of measurement were used to assess the effects of treatment, such as HbA1c, the mean difference (MD) with 95% CI was used.

Data synthesis – Data were pooled using the Mantel-Haenszel random-effects effects model for dichotomous outcomes and 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.[346] 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 Chi^2 tests. A $P < 0.05$ was used to denote statistical heterogeneity and 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.[346] We used conventions of interpretation as defined by Higgins et al. 2003.[350]

Assessment of publication bias – We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect versus standard error of the

effect size) when a sufficient number of studies were available (i.e., more than ten studies).[346] 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 that 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, stage of CKD, dialysis modality, age group (pediatric or elderly), and type of intervention, for example, short-acting versus long-acting GLP-1 RA. The test of subgroup differences used the I^2 statistic and a P-value of 0.1[346] (noting that this is a weak test).

Sensitivity analysis - 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 versus other), and country the study was conducted in.

However, insufficient data were available to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the quality of the evidence and 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.[347, 351] The GRADE approach 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. For observational studies, the initial quality of the evidence is low. 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, and 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, 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 one study)

all indicating concerns about the precision of the results.[351] The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 15).

For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from low quality of the evidence according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence see Table 16.

Table 15. Classification for certainty and quality of the of the evidence

Grade	**Quality of evidence**	**Meaning**
A	High	We are confident that the true effect lies close to that of 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 truth.

Table 16. GRADE system for grading quality of evidence

Study design	Staring grade of the quality of the evidence	Step 2 – Lower grade	Step 3 – raise grade for observational studies
RCTs	High	Study limitations: -1 serious -2 very serious	Strength of association +1 large effect size (e.g., 0.5) +2 very large effect size (e.g., 0.2)
	Moderate	Inconsistency: -1 serious -2 very serious	Evidence of a dose-response gradient
Observational studies	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	

Summary of findings tables

Summary of findings tables were developed to include a description of the population and the intervention and comparator. In addition, summary of findings tables included 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 are also provided in the summary of findings table. The summary of findings tables were generated using MAGICapp, an online software application designed to support guideline development, and are available in the Data Supplement.

Developing the recommendations

The recommendations were drafted by the Work Group Co-Chairs and Work Group members. Recommendations were revised in a multistep process during face-to-face meetings (New Orleans, United States of America, January 2019, and Barcelona, Spain, September 2019) and by email communication. The final draft was sent for external public review, reviewers provided open-ended responses. Based on feedback, it was further revised by Work Group Co-Chairs and members. All Work Group members provided feedback on initial and final drafts of the recommendation statement 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 recommendations

Grading the strength of the recommendations

The strength of a recommendation is graded as strong or weak (Table 17). 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 18).

Table 17. KDIGO nomenclature and description for grading recommendations

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

Table 18. 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 the evidence	A higher quality of the evidence, the more likely a strong recommendation is provided. However, there are exceptions where low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature where possible or were assessed in the judgment of the Work Group where robust evidence was not identified.
Resources and other considerations	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

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 the evidence – The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account relative importance for 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 two patients with diabetes and CKD. These members' unique perspective and lived experience, in addition to the Work Groups' understanding of patient preferences and priorities, also informed decisions about the strength of the recommendation. Qualitative evidence synthesis on patient priorities and preferences were not undertaken.

Resources and other considerations – Healthcare and non-health care resources, including all inputs in the treatment management pathway,[352] were considered in grading the strength of a recommendation. 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. However, the ERT conducted searches for systematic reviews of cost-effectiveness studies in support of selected topics of critical need.

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 used when no formal systematic evidence review was undertaken, or there was insufficient evidence to provide a graded recommendation. Practice Points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the stage of CKD, and use of therapies in specific subgroup populations. Practice Points were sometimes formatted as a Table, a Figure, or an Algorithm to make them easier to use in clinical practice

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (strong or weak) 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), rationale, and consideration for implementation. Each recommendation is linked to relevant summary of findings tables. An underlying rationale supported each practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. For a select number of clinical questions in this guideline, the ERT undertook a comprehensive evidence review beyond RCTs. However, these reviews were not exhaustive, as specialty or regional databases were not searched, and hand-searching of journals were not performed for these reviews. As such, observational studies relied on in some clinical questions, and in formulation of some recommendations, were not selected on the basis of a systematic search strategy. Two patients were members of the Work Group and provided an invaluable perspective and lived experience for the development of these guidelines. However, in the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature and formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, whilst resource implications were considered in formulation of recommendations, no economic evaluations were undertaken.

KDIGO CLINICAL PRACTICE GUIDELINE ON MANAGEMENT OF DIABETES IN CKD
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