

Saudi Clinical Practice Guidelines for management of diabetic kidney disease in adults

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ABSTRACT

Objectives: To develop evidence-based national guidelines incorporating recent advancements in clinical research and therapeutic strategies for the management of patients with diabetic kidney disease (DKD) in the Kingdom of Saudi Arabia (KSA).

Methods: We developed the guidelines using the GRADE methodology and a multidisciplinary expert panel comprising nephrologists, endocrinologists, clinical pharmacists, and methodologists across KSA. We conducted a systematic literature review of studies published between 2014–2024. The evidence certainty was evaluated across 5 domains using GRADEpro and categorized into 4 levels: “high”, “moderate”, “low”, and “very low”. Recommendations were formulated based on the benefit-risk ratio, evidence quality, and expert consensus, with a minimum agreement threshold of 70%.

Results: We established 39 evidence-based recommendations addressing key aspects of DKD management, including monitoring and treatment. Among the 39 recommendations, 6 focus on lifestyle interventions, 7 address glucose-lowering therapies, one discusses glycemic monitoring and targets, 8 address DKD evaluation and risk assessment, 7 emphasize comprehensive management approaches, and 10 discuss DKD pharmacological management. Two recommendations related to the comprehensive management of DKD were based on expert opinions owing to a lack of supporting evidence.

Conclusion: These Saudi national guidelines offer an evidence-based approach for managing DKD in adults with DM and provide a comprehensive framework for monitoring and treatment. Nevertheless, further local research and data collection are warranted to refine and enhance the guidelines’ effectiveness.

Keywords: Diabetic kidney disease, Diabetes mellitus, Management, Kingdom of Saudi Arabia

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Diabetes mellitus (DM) is a metabolic disease characterized by chronically elevated blood glucose levels.¹ The DM constitutes a global health concern that has attained epidemic levels in the Kingdom of Saudi Arabia (KSA), with a prevalence of 11.20% among the adult population.^{2,3} The elevated prevalence of DM in KSA presents a considerable public health challenge,

resulting in heightened risks of various consequences, such as cardiovascular illnesses, neuropathy, and chronic kidney disease (CKD).^{4,5}

The CKD is defined as the presence of structural or functional abnormalities that persist for at least 3 months, with a negative impact on health. It is classified based on the glomerular filtration rate (GFR) categories (≥ 90 , 60–89, 45–59, 30–44, 14–29, and < 15 l/min/1.73 m²) and persistent albuminuria categories (< 30 , 30–300, and > 300 mg/g).⁶ Among patients with DM, CKD is diagnosed based on the presence of albuminuria and/or decreased estimated glomerular filtration rate (eGFR) in the absence of signs or symptoms of other primary causes of kidney damage.⁷

Diabetic kidney disease (DKD) affects approximately 40% of patients with type 2 DM (T2DM) and 30% of those with type 1 DM.⁸ The DKD pathogenesis involves complex mechanisms initiated by hyperglycemia, including metabolic alterations, protein kinase C modifications, and hexosamine and polyol pathway changes; these processes trigger oxidative stress and inflammation, resulting in progressive kidney damage.^{9–11} The DKD is considered the predominant cause of end-stage kidney disease (ESKD) and significantly elevates the risk of developing numerous comorbid conditions, substantially reducing life expectancy among affected individuals.¹²

The DKD pathogenesis involves changes in renal hemodynamics, glomerular hypertension, hypoxia, ischemia, oxidative stress, and upregulation of the renin-aldosterone system.^{13,14}

Micro-proteinuria (microalbuminuria) was previously regarded as the clinical onset of DKD, with kidney function decline considered to begin only with the onset of overt proteinuria (macroalbuminuria). However, recent evidence has suggested that proteinuria does not always precede renal function loss in DM.¹⁵ The understanding of DKD has significantly evolved over time, with non-proteinuric DKD now recognized as a distinct phenotype, particularly among patients with T2DM.¹⁶

The high prevalence of DM in KSA has resulted in a corresponding increase in CKD risk, presenting a significant healthcare burden that warrants urgent attention.⁵ The CKD affects approximately 8.2% of the

population within the Middle Eastern region—slightly below the global average of 9.5%—with considerable geographic variation, ranging from 4.9% in Yemen to 12.2% in Lebanon.¹⁷ A previous Saudi study reported a CKD prevalence of 5.7, warranting immediate public health interventions to improve lifestyle practices, enhance early DM detection and management, and promote renal protective strategies to alleviate the long-term effects of this chronic condition.¹⁸

Therefore, the increased prevalence of DKD requires the conduct of comprehensive guidelines for appropriate disease management and treatment.

The recent years have seen substantial progress in CKD and DM management.^{19–21} Established recommendations, such as those from the Kidney Disease: Improving Global Outcomes (KDIGO) effort and the Kidney Disease Outcomes Quality (KDOQI) effort, have been revised to incorporate the most recent evidence-based approaches.^{19,20} These guidelines emphasize the importance of early identification, comprehensive care, and the utilization of novel therapeutic agents. Essential recommendations encompass strict blood pressure regulation, optimal glycemic control, and the use of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 (GLP-1) receptor agonists to mitigate renal disease progression and cardiovascular incidents.^{19,20}

We aimed to establish a systematic framework for patients with DKD through the Saudi DKD Guidelines. These guidelines are grounded in comprehensive literature evaluations, expert insights, and consensus-building processes, aiming to standardize therapy and improve patient outcomes and quality of life (QoL) by integrating the latest research and best practices.

Scope and purpose. These Saudi national guidelines provide evidence-based recommendations for managing DKD in patients with T2DM. The guidelines were developed to address the significant healthcare burden posed by the high DM prevalence in KSA and its associated increased CKD risk. Recent advancements in clinical research and therapeutic strategies were incorporated in these guidelines to provide comprehensive guidance for DKD monitoring and treatment.

Objectives. The goals of these guidelines are to establish a systematic framework for the management of patients with DKD in KSA across various clinical contexts, and to optimize patient care by integrating the latest research findings and best clinical practices to deliver the most beneficial care for the target populations. These guidelines aim to address the unique characteristics and needs of the Saudi healthcare system

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and patient demographic, with the overarching objective of improving patient outcomes by equipping healthcare providers with clear, practical recommendations for DKD management. Additionally, they seek to serve as a national reference for healthcare professionals, enabling the selection of the most suitable interventions and promoting cost-saving measures wherever possible.

Guidelines scope. The scope of these guidelines encompasses several key areas of clinical importance. Specifically, they address recommendations for monitoring kidney function and disease progression in adults with DKD in Saudi Arabia. They also outline evidence-based approaches to the pharmacological management of DKD, including glucose-lowering therapies, blood pressure control, lipid management, and strategies for cardiovascular risk reduction. In addition, the guidelines provide recommendations on the role of non-pharmacological interventions, such as lifestyle modifications, dietary adjustments, physical activity, and smoking cessation, in managing DKD. Finally, they cover guidance on risk assessment, appropriate evaluation methods, comorbidity management, and the timing and indications for initiating renal replacement therapies.

Target population. These Saudi national guidelines were primarily developed for managing DKD in adult patients with T2DM. This guideline is intended to support various healthcare providers involved in the management of DKD across KSA.

End-users. The end-users of these guidelines are nephrologists, endocrinologists, primary care and family medicine physicians, and clinical pharmacists in KSA. These guidelines provide valuable insights into DKD management, serving as a crucial resource for policymakers, researchers, and guideline developers.

How to use these guidelines. The Ministry of Health of KSA aims to provide clinicians and their patients with guidance for managing DKD in adults. When reviewing guidelines created using the Grading Recommendations, Assessment, Development, and Evaluation (GRADE) approach, it is essential to recognize that no guideline can fully address every aspect of an individual patient's case.

Each recommendation includes supporting statements that consider essential factors such as underlying ethical principles and patient preferences, resource requirements, practical implementation, equity considerations, patient tolerance, and other pertinent elements. These accompanying statements are vital for the accurate interpretation of the recommendations. Additionally, we emphasize that these guidelines should complement, rather than substitute for, clinical expertise

in routine practice. Healthcare providers must assess each patient's unique needs and circumstances when selecting optimal management approaches for diabetic kidney disease. This involves weighing impacts on clinical outcomes and evaluating the risk-benefit profile of diagnostic and treatment modalities while accounting for any relevant comorbidities or complications during guideline implementation in clinical settings.

Methods. The GRADE approach was used for the development of these guidelines.²² All statistical analyses are presented with 95% confidence intervals (95% CI) to indicate the precision of the estimates.

Panel composition. The Ministry of Health, KSA, initiated the guideline development process through the establishment of a multidisciplinary expert panel. The panel comprised 2 methodologists and 10 clinical experts with extensive clinical and academic experience in DKD. The panel members were selected based on their demonstrated expertise as nephrologists, endocrinologists, clinical pharmacists, and methodologists, ensuring comprehensive coverage of aspects related to DKD management. Among the panel members, 5 were nephrologists, 4 were pharmacists, one was an endocrinologist, and 2 were methodologists. There were 10 members from Riyadh (central region), one from Taif (western region), and one from Tabuk (northwest region). The average years of experience, publications, and treated patients per year were 16.8 years, 59 manuscripts, and 763 patients, respectively.

Group interaction and process. The guideline development process adhered to the GRADE methodology, facilitating systematic consensus-building and evidence synthesis. This methodological framework encompassed structured panel deliberations, systematic evidence evaluation, and transparent decision-making processes. The GRADE approach enabled the systematic evaluation of evidence certainty while minimizing potential bias through its structured assessment criteria and explicit consideration of factors influencing the strength of recommendations. All panel participants regularly participated in meetings and openly communicated to summarize the evidence, assess its reliability, and formulate recommendations.

Question selection and outcome prioritization. The guideline panel reviewed recent guidelines to identify key research questions for improving clinical management of DKD in KSA. Additionally, the panel utilized an iterative process to formulate new PICO questions in the Saudi Arabian healthcare context. After systematic deliberation, they prioritized and ratified 40 clinical questions.

Evidence synthesis. The study methodologists conducted a literature search to update the evidence supporting the previously published guidelines. Three medical databases (PubMed, EMBASE, and Scopus) were comprehensively searched. The search terms are available in **Supplementary File 1**. The time frame for the selected studies included those published between 2014 and 2024. However, we included articles published before 2014 in cases where there was insufficient evidence.

Two independent reviewers systematically screened the selected studies and evaluated titles and abstracts against predetermined inclusion criteria specific to each PICO question. Next, full-text assessments of potentially eligible articles were performed by the same reviewers to determine final study inclusion. If relevant systematic reviews were unavailable, we included RCTs or observational studies addressing our research questions (**Figure 1**).

We used “the Cochrane risk of bias tool” to assess potential sources of bias in RCTs and evaluate their quality,²³ whereas we assessed the quality of cohort observational studies using the Newcastle–Ottawa scale.²⁴

Assessing the certainty of evidence. Evidence tables were systematically generated using the GRADEpro Guideline Development Tool (GDT) for each PICO question,²⁵ incorporating critical outcomes. These profiles encompassed documentation of absolute and relative effect estimates alongside structured certainty assessments.

After assessing different GRADE domains (including “study design, risk of bias, publication bias, consistency in findings, indirectness of evidence, and imprecision of the estimate”), we categorized the certainty into “very low,” “low,” “moderate,” and “high”.²⁶ The classification of evidence certainty was defined as follows. High certainty evidence denotes substantial confidence that the actual effect lies near the effect estimate. Moderate certainty suggests moderate confidence, although the actual effect likely approximates the estimated effect. Low certainty evidence suggests limited confidence in the effect, with the possibility that the actual effect may substantially deviate from the forecast. Very low certainty evidence reflects minimal confidence in the effect estimate, with a high probability that the actual effect markedly differs from the estimated effect, warranting further research to reduce uncertainty.

Recommendations were formulated through systematic evaluation of the benefit-risk ratio, available evidence quality, and collective clinical expertise of panel members. The draft recommendations underwent

iterative refinement through structured virtual consultative sessions. Four structured consultative sessions, involving all panel members, were conducted via online meetings with a predefined structured agenda, enabling focused discussions, expert feedback, and continuous refinement to ensure the clarity, clinical relevance, and accuracy of the recommendations. The final recommendations were subjected to voting via the GRADEpro system. Since there is no specific criterion for consensus in the literature, with suggestions ranging from 51% to 80%, we adopted a predetermined threshold of 70% for agreement.^{27,28} The recommendations either favored the intervention or advised against it. Recommendation strength was systematically classified into 2 distinct categories: strong and conditional.²⁶ Differentiating recommendation strength is critical for clinical decision-making processes and implementation strategies (**Table 1**).

Recommendations.

1. Lifestyle interventions in patients with DKD:

Question 1. Should moderate-intensity physical activity vs a level compatible with their cardiovascular and physical tolerance be used for adults with T2DM and DKD?

Recommendation 1. For adults with T2DM and DKD, we suggest undertaking either moderate-intensity physical activity or a level compatible with their cardiovascular and physical tolerance (Conditional recommendation, moderate certainty evidence).

Remarks. Cumulative duration of at least 150 min per week.

Rationale. An RCT evaluated the effects of “moderate-intensity physical activity in adults with T2DM and DKD”.^{29,30} “Physical activity” resulted in reduced body weight (Mean difference [MD] 0.64 kg/m², [-3.68 to 2.39]; low certainty, **Table S2**) and hemoglobin A1C (HbA1c) (MD 0.44%, [-1.235 to 0.355]; low certainty, **Table S2**) and increased fasting insulin (MD 3.95 pmol/L, [-9.27 to 1.37]; low certainty, **Table S2**). Regarding lipid profiles, reductions in LDL (MD 0.46 mmol/L [-0.69 to -0.22]; moderate certainty, **Table S2**), triglycerides (MD 0.35 mmol/L, [-0.52 to -0.18]; moderate certainty, **Table S2**), and total cholesterol (MD 0.22 mmol/L, [-0.439 to -0.001]; moderate certainty, **Table S2**) were observed.²⁹ In another meta-analysis, the impact of “physical activity” on eGFR at a follow-up of 52 weeks assessed using the CKD Epidemiology Collaboration (CKD-EPI) creatinine-based equation revealed improvements (MD -1.76, [-7.5 to 3.99]; very low certainty, **Table S2**). Similarly, improvements were reported in the “CKD-EPI cystatin C-based equation” (MD -0.16, [-0.76 to 0.44]; very

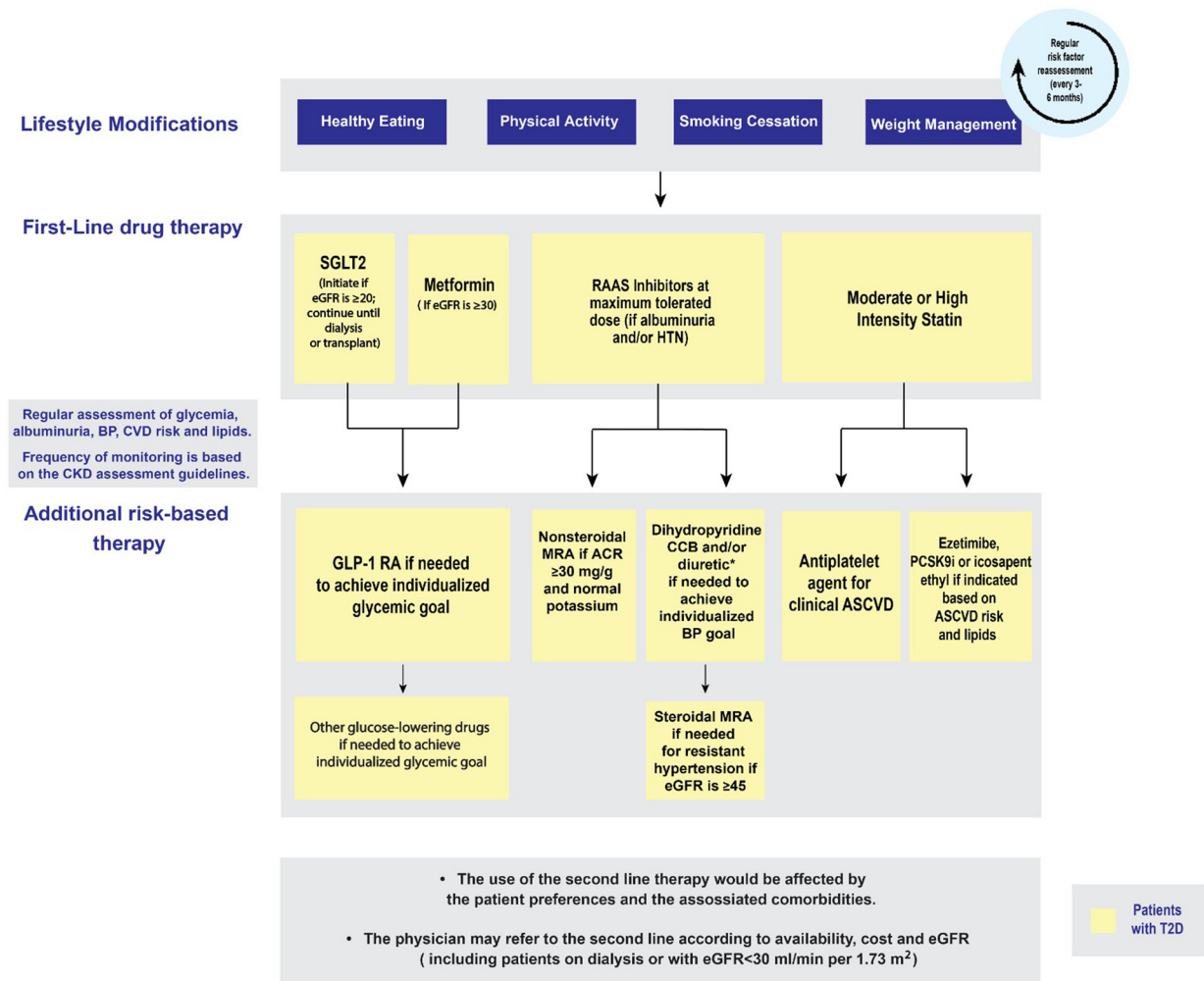


Figure 1 - Algorithm for DKD treatment. ASCVD: Atherosclerotic Cardiovascular Disease, BP: Blood Pressure, CVD: Cardiovascular Disease, DPP-4: Dipeptidyl Peptidase-4, eGFR: Estimated Glomerular Filtration Rate, GLP-1: Glucagon-Like Peptide-1, MRA: Mineralocorticoid Receptor Antagonist, PCSK9i: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor, RAAS: Renin-Angiotensin-Aldosterone System, SGLT2: Sodium-Glucose Cotransporter-2. *This algorithm is adapted from the American Diabetes Association guidelines.^{79,168}

low certainty, [Table S2](#)).³⁰ Moreover, physical activity resulted in decreased serum cystatin C at a follow-up of 52 weeks (MD -0.12 mg/L, [-0.39 to 0.15]; very low certainty, [Table S2](#)).³⁰

A pilot study demonstrated the feasibility and potential clinical benefits of exercise training programs in patients with obesity, DM, and CKD, demonstrating possible clinical effects on various kidney function tests, 24-hour protein excretion, hemoglobin, and lipid profiles.³¹

Population-level evidence consistently demonstrates that body mass index (BMI) serves as a reliable indicator of adiposity, with clinical significance extending beyond

simple weight classification. Research has established that adults maintaining a BMI $> 25 \text{ kg/m}^2$ (categorized as overweight or obese) face substantially elevated risks of developing multiple chronic conditions, including hypertension, cardiovascular disease (CVD), and CKD. The relationship with CKD appears dose-dependent, with higher BMI values correlating with progressively increasing kidney disease risk through multiple pathophysiological mechanisms, including glomerular hyperfiltration, systemic inflammation, oxidative stress, and metabolic dysregulation of the renin-angiotensin-aldosterone system (RAAS).³² The guideline panel

Table 1 - Strength of recommendations: Definitions and implications for stakeholders.

Strength of recommendation	Definition	Implications for stakeholders
Strong Recommendation	The benefits of the intervention clearly outweigh the risks, supported by high-quality evidence, and we recommend the intervention.	Clinicians should follow this recommendation in most cases. Patients can be assured of the benefits of the intervention.
Conditional Recommendation	The benefits of the intervention outweigh the risks, although the evidence is of low to moderate quality, and uncertainty remains; we suggest the intervention.	Clinicians should consider this recommendation, but individual patient circumstances and preferences should guide decision-making. Patients should be informed of the uncertainty in the decision-making process.
No Recommendation	Evidence is insufficient to recommend for or against the intervention. We do not recommend for or against the intervention.	Clinicians should use their judgment and consider patient preferences. Further research is needed to clarify the effectiveness of the intervention.
Weak Recommendation Against	The risks of the intervention outweigh the benefits; however, the quality of evidence is low, and we suggest against the intervention.	Clinicians should mostly avoid this intervention, but individual cases may warrant its use. Patients should be informed of the potential risks associated with the intervention.
Strong Recommendation Against	The risks of the intervention clearly outweigh the benefits, and the quality of evidence is high; we recommend against the intervention.	Clinicians should not use this intervention. Patients should be informed of the strong evidence against its use.

suggests that adults with T2DM and DKD engage in moderate-intensity physical activity tailored to their cardiovascular and physical tolerance. This approach helps manage blood glucose levels, reduce cardiovascular risk factors, and enhance overall well-being. However, customizing the exercise intensity to each individual's health status is crucial to ensure safety and effectiveness. This recommendation is similar to that issued by the KDIGO guidelines. It emphasizes the importance of providing guidance to patients with CKD using BMI while incorporating additional information such as dietary habits, comorbidity assessment, and laboratory value changes.¹⁹

Question 2. Should protein intake of less than 0.8 g/kg body weight vs 0.8 g/kg be used to slow the disease progression in adults with T2DM and DKD?

Recommendation 2. For adults with T2DM and DKD, we suggest maintaining a protein intake of 0.8 g/kg over an intake of less than 0.8 g/kg body weight (Conditional recommendation, moderate certainty evidence).

Rationale. Protein restriction may offer renal protection in CKD. Research suggests that lowering protein consumption below the known dietary recommendation of “0.8 g/kg/day” may potentially decrease glomerular hyperfiltration and slow disease progression. However, patients with DM are already advised to limit carbohydrates and fat, and further protein restriction may significantly reduce overall caloric intake, resulting in considerable weight loss and adversely impacting QoL. The risk of malnutrition due

to protein and calorie deficiency becomes concerning in populations or individuals with already low protein consumption. Importantly, adequate protein intake is crucial in DM management to prevent hypoglycemia, and excessive restriction increases the risk of these dangerous episodes.¹⁹

A meta-analysis of RCTs with moderate certainty evaluated the effects of a lower protein diet compared to “standard protein intake (0.8 g/kg)” in patients with diabetic nephropathy.³³ Regarding kidney function parameters, no difference was observed between “low-protein diet” and “standard protein intake” for GFR (weighted MD (WMD) -0.13 mL/min, [-2.63 to 2.38]; low certainty, Table S3), albuminuria (WMD -20.57 mg/24h, [-45.4 to 4.26]; very low certainty, Table S3), and serum creatinine level (WMD 0.01 mg/dL, [-0.08 to 0.1]; moderate certainty, Table S3). Regarding metabolic parameters, low protein intake reduced HbA1c (WMD -0.2%, [-0.39 to -0.01]; moderate certainty, Table S3), whereas no significant effects were observed in blood glucose levels (WMD 2.15 mg/dL, [-5.62 to 9.91]; low certainty, Table S3). No significant difference was observed in total cholesterol (WMD -2.29 mg/dL, [-17.04 to 12.47]; very low certainty, Table S3), LDL-C (WMD -1.26 mg/dL, [-12.16 to 9.63]; low certainty, Table S3), or triglyceride levels (WMD 3.73 mg/dL, [-11.84 to 19.3]; very low certainty, Table S3).³³

However, a recent study found that high protein restriction may result in malnutrition and other adverse health effects, particularly in patients with

already compromised nutritional status.³⁴ This study, alongside recent clinical investigations, has emphasized individualizing protein intake for patients undergoing hemodialysis through comprehensive risk-benefit assessments rather than standardized recommendations. This approach recognizes the variations in optimal protein requirements based on disease stage, residual kidney function, dialysis parameters, nutritional status, and comorbidities. While protein restriction may benefit earlier CKD stages, patients undergoing hemodialysis experience protein losses during treatment and increased catabolism, often requiring higher protein intake to prevent malnutrition. Therefore, protein requirements must be dynamically adjusted throughout treatment, particularly during illness or following surgical interventions.³⁴

A moderate protein intake aids in preventing malnutrition risk in patients with CKD, particularly in populations with traditionally low protein consumption.³⁵ A previous RCT on traditional protein intake (0.8g/kg), which included 60 patients, demonstrated that a protein-restricted diet may result in improved renal function in patients with T2DM and macroalbuminuria. The study offers evidence supporting the role of dietary protein modification in managing DKD complications.³⁶

Based on the WHO recommendation of “a protein intake of 0.8 g/kg” for the general population³⁷ and the risk of low-protein diets in adults with DKD, the guideline panel estimated that “protein intake of 0.8 g/kg body weight” is generally suggested to delay disease progression in such patients. This approach contributes to reducing the workload on the kidneys, potentially slowing the deterioration in kidney function and delaying ESKD onset. Moreover, the panel indicated that individual dietary needs should be carefully assessed as overly restrictive diets may not be suitable for all patients, particularly those having different nutritional backgrounds or CKD stages.¹⁹

Question 3. Should low sodium intake vs normal sodium intake be used for lowering the risk of DKD progression in patients with T2DM and DKD?

Recommendation 3. For adults with T2DM and DKD, we suggest low sodium over normal sodium intake (Conditional recommendation, very low certainty evidence).

Remarks. “Sodium intake” should be “<2 g of sodium per day (<90 mmol of sodium per day, or <5 g of sodium chloride per day)”, particularly in patients with increased blood pressure.

Rationale. For adults with T2DM and DKD, low sodium intake is suggested over normal sodium intake owing to the former’s significant benefits in managing

blood pressure and reducing kidney disease progression. Evidence indicates that sodium restriction can notably lower both systolic blood pressure (SBP) and diastolic blood pressure (DBP), which is crucial for preventing cardiovascular complications and slowing DKD progression.³⁸

A meta-analysis of 12 RCTs evaluated the effects of “a low-sodium diet” in patients with DKD through a moderate level of sodium restriction.³⁹ “Low-sodium intake” lowered SBP by 5.26 mmHg [-6.8 to -3.71]; low certainty, [Table S4](#) and DBP by 3.31 mmHg [-3.26 to -1.26]; low certainty, [Table S4](#). In addition, salt-restriction diet interventions reduced albumin excretion by 12.62 units in patients with microalbuminuria [-19.64 to -5.6]; low certainty, [Table S4](#) and 123.07 units in those with macroalbuminuria [-166.21 to -79.94]; very low certainty, [Table S4](#). The overall albumin excretion rate decreased by 15.47 units [-22.4 to -8.54]; very low certainty, [Table S4](#).³⁹

This evidence concluded that patients with DM or evidence of kidney disease should limit “salt intake to <5 g/day”.³⁹

Research examining salt consumption in the broader population has revealed that elevated sodium intake is associated with higher death rates from CVD and overall mortality.⁴⁰ The KDIGO guidelines recommend that sodium intake be <2 g. Moreover, these guidelines recommend combining sodium restriction with strategies to reduce CVD risk for patients with CKD. Nevertheless, this sodium restriction recommendation requires modification for specific patient populations, particularly those suffering from malnutrition or residing in regions with high ambient temperatures, where strict sodium limitation may prove counterproductive or potentially harmful.¹⁹

While low sodium intake is generally beneficial, some researchers argue that overly restrictive diets may result in nutritional deficiencies or adverse effects, particularly in vulnerable populations. Therefore, the guideline panel suggests balancing sodium intake with overall nutritional needs, which is essential to optimize health outcomes.

Question 4. Should weight reduction vs no weight reduction be used in adults with T2DM and DKD?

Recommendation 4. For adults with T2DM and DKD, we suggest weight reduction to achieve the ideal BMI over no weight reduction (Conditional recommendation, very low certainty evidence).

Rationale. Obesity is “characterized by a BMI >30 kg/m²” and constitutes a factor contributing to CKD progression.⁴¹ Research specific to Asian populations has established that individuals with a BMI >27.5

kg/m² face heightened vulnerability to negative health consequences.⁴² Moreover, a comprehensive international analysis incorporating data from approximately 5.5 million adults across 40 nations demonstrated that excess adiposity—whether measured by BMI, abdominal circumference, or waist-to-height proportions—independently predicts deteriorating kidney function and increased mortality risk, regardless of whether baseline glomerular filtration rates are within normal ranges or already compromised.⁴³

A previous RCT evaluated consecutive patients with T2DM with confirmed nephropathy and a BMI >25 kg/m², classifying participants into three different groups: Group A received angiotensin-converting enzyme inhibitors (ACEI) therapy, Group B followed strict lifestyle modification guidelines for weight loss, and Group C was treated with the anti-obesity drug Orlistat.⁴⁴ This RCT demonstrated that while all interventions likely had some benefit, ACEIs appeared more effective in reducing proteinuria than lifestyle modifications alone (MD 205.47 g/day, [-501.89 to 912.83], very low certainty, [Table S5](#)). This suggests that while weight loss may be beneficial, other interventions, such as ACEIs, may be more effective in managing proteinuria.⁴⁴

Weight loss via bariatric surgery reduced albuminuria in 6 studies of patients with CKD and decreased GFR in 6 studies of patients with hyperfiltration, with one study showing increased GFR in patients with CKD stages 3–4 (very low certainty, [Table S5](#)).⁴⁵ Weight loss using anti-obesity agents was assessed in 6 non-randomized studies, with decreased GFR in four studies and reduced albuminuria in 3 (very low certainty, [Table S5](#)). Dietary changes, either alone or in combination with lifestyle modifications, were evaluated in 11 non-randomized studies. The impact on GFR varied considerably across studies examining patients with hyperfiltration, with 2 investigations reporting increased GFR, four showing stable measurements, and 2 demonstrating decreased filtration rates. Similarly, kidney damage markers showed heterogeneous responses, although generally positive trends emerged: six studies documented reductions in albuminuria, with one showing no change, whereas five separate investigations noted decreased proteinuria levels following intervention (low to very low certainty, [Table S5](#)).⁴⁵ These findings underscore the potential benefits of weight loss interventions on kidney function and proteinuria, although evidence certainty remains low to very low.

Our recommendation aligns with the KDIGO guidelines,⁴⁶ which indicate that healthcare providers should evaluate patients' desire to initiate weight loss

and suggest increased activity along with a suitable diet, particularly when the eGFR exceeds “30 mL/min per 1.73 m²”. Moreover, a higher BMI has been linked to improved outcomes in patients undergoing dialysis; hence, whether purposeful weight loss yields health benefits for this group remains uncertain.⁴⁷ Consequently, clinical recommendations for deliberate weight reduction should be carefully tailored, as such interventions may be inappropriate or potentially counterproductive for specific subgroups of patients with late-stage CKD. The panel recognizes that a multidisciplinary supervised nutrition care and shared decision-making approach to weight management should be individualized to each patient's needs, age, preferences, existing comorbidities, and goals. It might include either one form or a combination of a balanced diet, lifestyle modifications and regular physical activity, bariatric surgery, or anti-obesity agents.⁴⁶

The guideline panel acknowledges the very low certainty of evidence directly supporting weight loss for DKD outcomes. Nevertheless, the panel suggests weight reduction based on the broader benefits of weight management in T2DM and the potential for improved kidney health, estimating it as moderately cost-saving and cost-effective. Moreover, the panelists determined that the intervention is unlikely to have a significant impact on equity and considered it a potentially acceptable and feasible option.

Question 5. Should medical nutrition therapy (MNT) vs no MNT be used for adults with T2DM and DKD?

Recommendation 5. For adults with T2DM and DKD, we suggest using MNT over no MNT (Conditional recommendation, very low certainty evidence).

Rationale. Our evidence is based on a meta-analysis (n=1227) of 11 studies.⁴⁸ The studies evaluated the effectiveness of MNT prescribed by registered dietitians in patients with DM compared to control groups receiving usual care.

In a synthesis of data from the RCTs, reductions in fasting blood glucose (8 trials; WMD 8.85 mg/dL lower, [-14.41 to -3.28]; low certainty, [Table S6](#)), HbA1c (8 trials; WMD 0.43% lower, [-0.69 to -0.17]; low certainty, [Table S6](#)), weight (6 trials; WMD 1.54 kg lower, [-2.44 to -0.64]; low certainty, [Table S6](#)), BMI (6 trials; WMD 0.34 kg/m² lower, [-0.52 to -0.17]; low certainty, [Table S6](#)), and waist circumference (5 trials; WMD 2.16 cm lower, [-4.09 to -0.23]; very low certainty, [Table S6](#)) were observed.⁴⁸

Regarding lipid profiles, cholesterol (8 trials; WMD -4.06 mg/dL, [-7.31 to -0.81]; low certainty, [Table S6](#)) and triglycerides (6 trials; WMD -8.82 mg/dL, [-20.1

to 2.45]; very low certainty, [Table S6](#)) significantly decreased, whereas “LDL and high-density lipoprotein” decreased without significant differences (4 trials; WMD -4.43 mg/dL, [-13.66 to 4.8]; very low certainty, and 6 trials; WMD 0.4 mg/dL lower, [-3.2 to 2.4]; very low certainty, [Table S6](#), respectively). The results showed a significant decrease in blood pressure: SBP decreased by 7.9 mmHg (7 trials; [-13.03 to -2.77]; very low certainty, [Table S6](#)) and DBP by 2.6 mmHg (7 trials; [-4.27 to -0.94]; very low certainty, [Table S6](#)). While the meta-analysis did not specifically focus on DKD outcomes, the observed glycemic control, blood pressure, and lipid profile outcomes are important for managing DKD progression. These improvements can reduce the strain on the kidneys and potentially slow kidney function decline. However, these indications were limited by serious concerns regarding bias, inconsistency, and potential publication bias.

Protein-energy wasting affects 11–50% of adults and 20–45% of specific populations in various global regions.⁴⁹ The risk of protein-energy wasting rises as CKD advances and is further influenced by DM, autoimmune disorders, and CVD.⁵⁰ The pathogenesis of protein-energy wasting likely constitutes dual mechanisms involving appetite suppression induced by accumulated uremic toxins and persistent inflammatory processes characterizing advanced kidney disease.⁵⁰ Individuals with CKD require “nutritional assessment and intervention from a renal dietitian or a qualified nutrition provider,” according to the guidelines on undernutrition in CKD, owing to its effects on prognosis and QoL.⁵¹ However, MNT can be resource-intensive, requiring access to registered dietitians and patient commitment. These factors led the panel to issue a conditional recommendation, suggesting MNT for adults with T2DM and DKD but acknowledging that the benefits and harms must be carefully weighed based on individual circumstances.

Moreover, the panel concluded that the intervention is unlikely to significantly impact equity and considered it a potentially acceptable and feasible option.

Question 6. Should continued smoking vs smoking cessation be used for reducing the risks of developing and progressing DKD and CVD among adults with T2DM and DKD?

Recommendation 6. For adults with T2DM and DKD, we suggest smoking cessation over no smoking cessation (Conditional recommendation, very low certainty evidence).

Rationale. Evidence regarding smoking cessation in patients with DKD remains lacking. Therefore, this recommendation was based on a small, controlled, randomized, cross-over study (n=25),⁵² the known harms

of smoking, and the panel members’ clinical experience. The study had a short timeframe, comparing “8 h of controlled smoking” with “8 h of nonsmoking” on separate days. The heart rate was significantly increased in the smoking group (MD 6.6, [2.0 to 11.5], $p=0.003$; very low certainty, [Table S7](#)). Moreover, blood pressure was higher during smoking in patients with DM without autonomic neuropathy (MD 7.9, [1.7 to 14.1] mmHg, $P=0.018$ and MD 2.5, [1.6 to 6.6] mmHg; $P=0.204$, respectively; very low certainty, [Table S7](#)).⁵²

Proteinuria significantly increased during smoking among patients with DM without autonomic neuropathy (MD 8.1, [0.3 to 52.2] mg mmol-1 creatinine, $p=0.002$; very low certainty, [Table S7](#)).⁵²

Smoking is a risk factor for CKD development and contributes to increased CVD risk among patients with CKD.⁵³ A study indicated a higher incidence of CVD in current smokers compared to former smokers among patients with CKD.⁵⁴

Considering the benefits and feasibility of smoking cessation, the guideline panel emphasizes the importance of advising patients with DKD to stop smoking.

The key recommendations issued by the panel for lifestyle interventions in patients with DKD are listed in [Table 2](#).

2. Glycemic Monitoring in Patients with DKD:

Question 7. Should optimal glycemic control (achieving HbA1c <7%) vs less intensive glycemic control be used to reduce the risks of the development and progression of DKD and CVD among adults with T2DM and DKD?

Recommendation 7. For adults with T2DM and DKD, we suggest using either optimal (HbA1c <6.5% or 7%) or less intensive glycemic control (HbA1c <7.5% or 8.0%) to reduce the risk of developing and progressing DKD and CVD (Conditional recommendation, low certainty evidence).

Rationale. Our recommendation is based on a meta-analysis and a retrospective cohort study.^{55,56} The meta-analysis of 27391 adult patients with T2DM and CKD worldwide compared less intensive control using “anti-diabetic drugs and/or insulin” with “optimal control with dietary measures”.⁵⁵ The cohort study evaluated 4543 patients with CKD and T2DM to assess whether baseline HbA1c levels and HbA1c trajectories are linked with the risk of ESKD and mortality.⁵⁶

In the cohort study, no significant difference was observed in ESKD progression between patients with DM with optimal glucose control and those with HbA1c levels between 7-9% (Hazard ratio [HR] 1.00, [0.93 to 1.07]; very low certainty, [Table S8](#)). However, “all-cause mortality” was higher among patients with

less intensive control (HbA1c level >9%) compared to those with optimal control (HbA1c level <7%) (HR 1.25, [1.07 to 1.46]; very low certainty, [Table S8](#)).⁵⁶

In the meta-analysis, intensive glycemic control did not affect the risk of serum creatinine doubling (OR 0.98, [0.81 to 1.19]; very low certainty, [Table S8](#)) or need for dialysis (OR 0.84, [0.69 to 1.02]; very low certainty, [Table S8](#)); nevertheless, the risk of death from kidney failure was lower in the intensive glycemic control group (OR 0.62, [0.39 to 0.98], low certainty, [Table S8](#)).⁵⁵

Considering the limited reliability of available evidence and the potential for adverse events associated with stringent management approaches, the panel suggests individualizing glycemic targets within a reasonable range. Less intensive targets may be appropriate for older adults, those with frailty, advanced renal disease, or those with multiple comorbidities, long-standing DM, or a history of severe hypoglycemia. Conversely, more intensive targets may be considered in younger, healthier individuals with few comorbidities, mild-to-moderate CKD, and longer life expectancy.

The KDIGO guidelines emphasize the critical need to set optimal glycemic targets for patients with DM on dialysis, ensuring the prioritization of their health and well-being during treatment.⁴⁶ The glycemic monitoring recommendation suggested by the panel is presented in [Table 3](#).

3. Glucose-Lowering Therapies in patients with DKD:

Question 8. Should SGLT-2i vs no SGLT-2i be used for adults with T2DM and DKD?

Recommendation 8. For adults with T2DM and DKD, we recommend using SGLT-2i over no SGLT-2i (Strong recommendation, moderate certainty evidence).

Rationale. Our recommendation aligns with 2 meta-analyses.^{57,58} The first one included 14 RCTs involving “patients with CKD with and without T2DM” and evaluated the cardiovascular and kidney outcomes of SGLT-2i.⁵⁷ SGLT-2i was associated with a significant reduction in the risk of composite CVD and renal outcomes (HR 0.72, [0.67 to 0.77], and HR 0.65, [0.59 to 0.71]; moderate certainty, [Table S9](#)). Furthermore, SGLT-2i was associated with the reduction of risks of “all-cause mortality,” “cardiovascular death,” and “hospitalization for heart failure” (HR 0.87, [0.77 to 0.99], HR 0.85, [0.77 to 0.94], and HR 0.61, [0.55 to 0.68], respectively; moderate certainty, [Table S9](#)). Nevertheless, the analysis showed no statistically significant reduction in major adverse cardiovascular events among patients receiving SGLT-2is compared to those administered placebo (HR 0.86, [0.74 to 1.02]; low certainty, [Table S9](#)).⁵⁷

The other meta-analysis included 14 RCTs with 59874 “elderly patients with T2DM and DKD” and evaluated the effectiveness of SGLT-2i at any dose compared to placebo.⁵⁸ No significant difference was reported in eGFR (MD 0.7, [-0.51 to 1.92]; very low certainty, [Table S9](#)) and hypoglycemia risk (RR 0.97, [0.93 to 1.01], low certainty, [Table S9](#)). The overall incidence of “adverse events” and “the risk of acute kidney injury” were significantly reduced after using SGLT-2i compared to placebo (RR 0.97, [0.95 to 0.99]; low certainty, [Table S9](#); and RR 0.77, [0.70 to 0.86];

Table 2 - Strength and level of evidence for the lifestyle intervention recommendations in patients with DKD:

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
1. For adults with T2DM and DKD, we suggest undertaking either “moderate-intensity physical activity” or a “level compatible with their cardiovascular and physical tolerance”. Remarks: “Cumulative duration of at least 150 min per week.”	Conditional	Moderate	100%
2. For adults with T2DM and DKD, we suggest maintaining “a protein intake of 0.8g/kg” over an “intake of less than 0.8g/kg body weight”.	Conditional	Moderate	100%
3. For adults with T2DM and DKD, we suggest low sodium over normal sodium intake. Remarks: “Sodium intake” should be “<2 g of sodium per day (<90 mmol of sodium per day, or <5 g of sodium chloride per day)”, particularly in patients with increased blood pressure.	Conditional	Very low	100%
4. For adults with T2DM and DKD, we suggest weight reduction to achieve the ideal BMI.	Conditional	Very low	100%
5. For adults with T2DM and DKD, we suggest using MNT over no MNT.	Conditional	Very low	100%
6. For adults with T2DM and DKD, we suggest smoking cessation over no smoking cessation.	Conditional	Very low	100%
BMI: Body mass index, DKD: Diabetic kidney disease, MNT: Medical nutrition therapy, T2DM: Type 2 diabetes mellitus			

moderate certainty, [Table S9](#)). However, increased risks of urinary tract infections (UTIs) (RR 1.06, [1.00 to 1.11]; low certainty, [Table S9](#)), diabetic ketoacidosis (RR 2.25, [1.57 to 3.24], low certainty, [Table S9](#)), and “genital mycotic infections” (RR 3.47, [2.97 to 4.04], low certainty, [Table S9](#)) were reported in the SGLT-2i group.⁵⁸

These differences between the studies may be attributed to differences in study populations and the follow-up duration. The panel judged that SGLT-2i benefits outweigh the potential harms.

The SGLT-2i reduces the risk of kidney disease progression and ESKD in DKD, regardless of urinary protein levels. Patients with high-severity albuminuria, defined as “an albumin-to-creatinine ratio (ACR) ≥ 300 mg/g,” exhibit a significantly elevated risk of kidney disease progression and thus derive greater absolute benefits from SGLT-2i therapy. In contrast, patients with normal albumin levels or moderately increased albuminuria have a lower absolute risk of progression and hence experience comparatively smaller absolute benefits from treatment.^{59,60}

The moderate certainty of the evidence for these key benefits, combined with the feasibility, acceptability, and moderate costs of SGLT-2i, led the panel to strongly endorse their use in adults with T2DM and DKD. The KDIGO guidelines recommended SGLT-2i as a first-line treatment option for managing glycemic control in “patients with T2DM and DKD”.^{19,46} Moreover, the guidelines suggest treatment with an SGLT2i should be maintained once started, even if the eGFR drops “below 20 mL/min per 1.73 m²”.¹⁹ The KDIGO guidelines emphasize that initiating or continuing SGLT2i therapy does not necessitate changing the frequency of CKD monitoring. Additionally, the temporary decline in eGFR observed at treatment initiation is typically not a reason to discontinue therapy.¹⁹

Question 9. Should SGLT-2i vs Sulfonylurea be used for Adults with T2DM and DKD?

Recommendation 9: For adults with T2DM, DKD, and an eGFR >20 mL/min per 1.73 m², we recommend

using an SGLT-2i over Sulfonylurea, regardless of glycemic control levels (Strong recommendation, moderate certainty evidence).

Rationale. A network of 5 RCTs (n=24276) compared SGLT-2i to sulfonylureas in patients with T2DM.⁶¹ While this analysis did not specifically focus on patients with DKD and the specified eGFR, it provides valuable insights. Specifically, SGLT-2i showed reductions in mortality (OR 0.75, [0.62 to 0.92]; absolute risk reduction 1.88%; moderate certainty, [Table S10](#)), “major adverse cardiovascular events” (OR 0.85, [0.71 to 1.02]; absolute risk reduction 1.59%; moderate certainty, [Table S10](#)), and “hospitalization for heart failure” (OR 0.77, [0.56 to 1.07]; absolute risk reduction 0.64%; moderate certainty, [Table S10](#)).⁶¹

In another study, patients who initiated SGLT-2i were more likely to adhere to treatment (OR 1.364, [1.30 to 1.43], $p<0.001$) and persist with the therapy (HR 0.746, [0.71 to 0.78], $p<0.001$) compared to those who newly initiated treatment with sulfonylureas.⁶²

A cohort study of 75739 participants with T2DM concluded that SGLT-2i was more effective than sulfonylureas in reducing HbA1c levels (MD -2.5 mmol/mol, [-3.7 to -1.3]), BMI (MD -1.6, [-1.7 to -1.4]), SBP (MD -2.1, [-3.1 to -1.0]), and “kidney disease progression” (HR 0.42, [0.22 to 0.81]) over one year.⁶³

While sulfonylureas effectively lower blood glucose, they present the risk of hypoglycemia, which can be particularly dangerous in DKD. Conversely, the SGLT-2i medication class demonstrates a reduced propensity for causing hypoglycemia while simultaneously providing supplementary advantages for heart and kidney protection.^{64,65}

Substantial clinical evidence consistently demonstrates that SGLT-2is effectively attenuate DKD progression while simultaneously decreasing CVD occurrence. These agents potentially diminish major cardiovascular event frequency in patients with atherosclerotic CVD. Additionally, SGLT-2is demonstrate significant benefits in preventing heart failure hospitalizations, reducing mortality among

Table 3 - Strength and level of evidence for the glycemic monitoring recommendations in patients with DKD:

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
7. For adults with T2DM and DKD, we suggest using either optimal (HbA1c $<6.5\%$ or 7%) or less intensive glycemic control (HbA1c $<7.5\%$ or 8.0%) to reduce the risk of developing and progressing DKD and CVD.	Conditional	Low	100%

CVD: Cardiovascular disease, DKD: Diabetic kidney disease, HbA1c: Hemoglobin A1c, T2DM: Type 2 diabetes mellitus

patients with HF, and decreasing overall death rates across patient populations.⁶⁶

Furthermore, recent evidence from the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials has demonstrated that cardiovascular and renal outcomes were improved with SGLT2i among patients with an eGFR of 20 mL/min/1.73 m² or lower, with no significant glucose-lowering effects.⁶⁷

Based on the evidence, the panel strongly recommends SGLT-2i over sulfonylureas in “adults with T2DM, DKD, and eGFR $\geq$ 20 mL/min/1.73 m²,” regardless of baseline glycemic control. The KDIGO guidelines suggest using SGLT-2i as first-line therapy and sulfonylureas as an additional drug therapy. They also emphasized that once SGLT2i is initiated, it can continue even if eGFR falls below 20 mL/min/1.73 m², unless it is intolerable or kidney replacement therapy begins.⁴⁶

Question 10: Should SGLT-2i vs. Metformin be used for Adults with T2DM and DKD?

Recommendation 10: *For adults with T2DM and DKD who have not met their individualized glycemic targets, we recommend using SGLT-2i over metformin (Strong recommendation, moderate certainty evidence).*

Remarks. If further glycemic control is necessary, consider combining it with metformin.

Rationale. This recommendation was based on a meta-analysis comparing SGLT-2i to metformin among “patients with T2DM and DKD”.⁶⁸ Based on 3 trials (n=1270), no significant difference was observed between SGLT-2i and metformin regarding “all-cause mortality” and “the risk of hospitalization” for HF (OR 0.39, [0.07 to 2.01], and OR 0.087, [0.0035 to 2.174]; moderate certainty, **Table S11**).⁶⁸

However, other studies indicated that SGLT-2i reduced CKD progression, dialysis, transplantation, and cardiovascular events, particularly HF or death from kidney disorders.^{69,70}

Considering that the use of SGLT-2i is effective, acceptable, and likely feasible, the panel recommends using SGLT-2i over metformin.

Considering that combining SGLT-2i and metformin is safe and effective.^{20,71} The panel recommends using this combination if further glycemic control is necessary. However, it should be noted that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m². Annual monitoring of eGFR is recommended for patients on metformin. When eGFR falls below 60 mL/min/1.73 m², more frequent checks (every 3-6 months) are advisable. Dose adjustments, such as halving the maximum dose, should be considered if eGFR drops below 45 mL/min/1.73 m².

For some patients with conditions predisposing them to hypoperfusion and hypoxemia, a dose reduction may also be needed if eGFR is between 45 and 59 mL/min/1.73 m².⁴⁶

Question 11. Should GLP-1 receptor agonist treatment vs. no treatment be used for slowing disease progression in adults with T2DM and DKD?

Recommendation 11. *In adults with T2DM and DKD, we recommend using GLP-1 receptor agonists over not using them to slow CKD progression, reduce albuminuria, and achieve glycemic control (Strong recommendation, moderate certainty evidence).*

Remarks. GLP-1 receptor agonists are preferred for patients with an eGFR $\geq$ 25 mL/min in patients with obesity and individuals with heart failure and preserved ejection fraction.

Rationale. GLP-1 receptor agonists have demonstrated cardiac and kidney protection in recent studies. They demonstrated significant renoprotective effects independent of their “glucose-lowering properties,” slowed the eGFR decline, and reduced the risk of composite kidney outcomes in patients with DKD.^{72,73}

A meta-analysis of 57830 participants demonstrated that “GLP-1 receptor agonists” have a positive effect on kidney-related outcomes, significantly reducing the risk of developing “composite kidney disease” (Relative risk [RR] 0.82, [0.73 to 0.93]; moderate certainty, **Table S12**). Additionally, they significantly reduced the risk of kidney failure compared to the placebo (HR 0.84, [0.72 to 0.99]; high certainty, **Table S12**). “GLP-1 receptor agonists” were linked to a lower risk of worsening kidney function than placebo (HR 0.79, [0.68 to 0.92]; moderate certainty, **Table S12**).⁷⁴

The meta-analysis provided data focusing on cardiovascular outcomes, with a total of 67,769 patients, demonstrating reduced “major adverse cardiovascular events” with GLP-1 receptor agonist treatment, without statistical significance (HR 0.79, [0.57 to 1.10]; moderate certainty, **Table S12**). “GLP-1 receptor agonists” showed a significant protective effect for cardiovascular death (HR 0.86, [0.80 to 0.92]; high certainty, **Table S12**). Moreover, they resulted in decreased risks of “non-fatal myocardial infarction” (HR 0.90, [0.82 to 0.99]; moderate certainty, **Table S12**) and non-fatal stroke (HR 0.87, [0.79 to 0.96]; high certainty, **Table S12**). Additionally, “GLP-1 receptor agonists” significantly reduced “hospitalization for heart failure” (HR 0.87, [0.81 to 0.95]; high certainty, **Table S12**) and “all-cause death” (HR 0.88, [0.83 to 0.93]; high certainty, **Table S12**).⁷⁴

Accumulating evidence from RCTs demonstrates that “GLP-1 receptor agonists” confer significant

cardioprotective effects in patients with elevated cardiovascular risk profiles while simultaneously mitigating hypoglycemic events by attenuating CKD progression. The pleiotropic mechanisms of “GLP-1 receptor agonists” include anti-inflammatory actions, enhanced endothelial function, and favorable hemodynamic modulation, contributing to their efficacy in reducing “major adverse cardiovascular events” and preserving renal function, particularly in patients where atherosclerotic CVD represents the predominant pathophysiological concern in their comprehensive DM management algorithm.^{75,76}

Recently, the FLOW trial has assessed the impact of subcutaneous semaglutide on renal and cardiovascular outcomes among patients with T2DM and DKD compared with placebo. Semaglutide was associated with a significant reduction in renal and cardiovascular events, including a persistent reduction of $\geq 50\%$ from baseline in eGFR, persistent eGFR < 15 mL/min/1.73 m², and initiation of kidney replacement therapy. The risk of major cardiovascular events was reduced by 18% and the risk of death was lower by 20%.⁷⁷

Obesity is present in most patients with T2DM, and weight management is essential among these patients. In this context, GLP-1 receptor agonists are often preferred for managing obesity owing to their dual benefits of glycemic control and substantial weight reduction. Clinical studies have demonstrated significant reductions in BMI and waist circumference in “patients treated with GLP-1 receptor agonists”.⁷⁸

Considering multiple factors, including the benefits strongly outweighing potential risks, “GLP-1 receptor agonists” are likely to be an acceptable and feasible therapeutic option to most stakeholders; therefore, the panel issued a strong recommendation for GLP-1 receptor agonist use. Additionally, the ADA (2025) and KDIGO guidelines acknowledge the renal and cardiovascular benefits of these agents.^{46,79}

Question 12. Should adding GLP-1 receptor agonists to SGLT-2i treatment vs. SGLT-2i treatment alone be used in adults with T2DM and DKD?

Recommendation 12. For adults with T2DM and DKD, we suggest adding GLP-1 receptor agonists to SGLT-2i for patients who have not achieved the proteinuria target or glycemic control or those with increased cardiovascular risk (Conditional recommendation, low certainty evidence).

Rationale. An RCT (n=60) compared the addition of “GLP-1 receptor agonists to SGLT-2is in patients with T2DM and albuminuria.” “Addition of GLP-1 receptor agonists” resulted in a significant reduction in “the urinary albumin-creatinine ratio” and HbA1c

(MD -22 mg/g, [-44 to 10], and MD -8 mmol/mol, [-13 to -3], respectively; low certainty, [Table S13](#)). No significant difference was observed in 24-hour SBP (MD -2 mmHg, [-10 to 5]; low certainty, [Table S13](#)). A minor improvement in eGFR was observed in the group that received “GLP-1 receptor agonists” alongside SGLT-2is compared to the placebo group (MD 3.9 mL/min/1.73 m², [-3.6 to 11.6]; low certainty, [Table S13](#)). However, an increased risk of adverse events was reported when “GLP-1 receptor agonists” were added to SGLT-2is (RR 2.20, [0.86 to 5.56]; risk increase was 200 per 1,000, [23 to 760]; low certainty, [Table S13](#)).⁸⁰ Furthermore, a meta-analysis concluded that the combination did not increase severe hypoglycemia incidence compared to monotherapy with “GLP-1 receptor agonists alone” or “SGLT-2is alone” (OR 1.38, [0.14 to 13.14] and OR 2.39, [0.47 to 12.27], respectively).⁸¹ Additionally, another meta-analysis (n=1604 patients with T2DM or obesity) indicated that adding SGLT-2is to GLP-1 receptor agonists significantly lowered “cardiovascular events incidence” (RR 0.19, [0.04 to 0.96]).⁸²

“GLP-1 receptor agonists” represent the optimal choice for therapeutic intensification in “patients with DM and CKD” who continue to exhibit albuminuria or maintain poorly controlled metabolic parameters—including suboptimal blood glucose levels, elevated blood pressure, or excess weight—despite ongoing “SGLT-2i treatment.” Despite the potential clinical benefits of the drug combination for patients with T2DM, several factors may restrict its adoption, including reimbursement issues and the costs of multiple treatments. Therefore, treatment using “GLP-1 receptor agonists” and “SGLT-2i combination therapy” should be individualized, considering patient preferences and any other related comorbidities.^{20,83}

The panel deemed that the balance between desirable and undesirable effects likely favors combination therapy. However, adding GLP-1 receptor agonists to SGLT-2is would incur large costs.

Question 13: Should long-acting GLP-1 receptor agonists vs. Dipeptidyl peptidase 4 (DPP-4) inhibitors be used for adults with T2DM and DKD who have not achieved individualized glycemic targets despite using metformin and SGLT-2i?

Recommendation 13: For adults with T2DM and DKD who have not achieved individualized glycemic targets despite using metformin and SGLT-2i, we suggest using long-acting GLP-1 receptor agonists over DPP-4 inhibitors (Conditional recommendation, low certainty evidence).

Rationale. Regarding long-acting “GLP-1 receptor agonists” vs “DPP-4 inhibitors,” a network meta-

analysis containing 16 trials with 46,292 patients showed potential benefits of “GLP-1 receptor agonists” for reduced kidney-specific composite outcomes, major adverse cardiovascular events, and hospitalization for HF compared to “DPP-4 inhibitors” (HR 0.87, [0.70 to 1.09]; HR 0.85, [0.73 to 0.99], and HR 0.82, [0.64 to 1.05], respectively; low certainty, Table S14).⁸⁴

“GLP-1 receptor agonists” improve glycemic control among patients with T2DM and have associated beneficial effects on DKD. In addition, they can be used for weight management and to reduce cardiovascular risk.^{85–87} Regarding cost-effectiveness, the cost comparison between the interventions reveals significant economic implications for treatment choices.⁸⁸

Therefore, the guideline panel issued that “GLP-1 receptor agonists” are important for managing T2DM, particularly in patients who additionally have DKD. SGLT-2is have a limited glucose-lowering effect, particularly in patients with reduced eGFR, and patients with glycated hemoglobin levels significantly above their target may require additional glucose-lowering treatments.

Among various glucose-lowering medications, the GLP-1 receptor has several benefits in individuals with preexisting cardiovascular or kidney conditions.⁸⁹ Therefore, adding a “GLP-1 receptor agonist” can enhance glycemic control and offer further benefits for patients with T2DM and DKD who have not achieved adequate glycemic control despite initial treatment. This recommendation is similar to that by the KDIGO guidelines.¹⁹ The guideline panel supports the application and generalization of “GLP-1 receptor agonists” as an acceptable and feasible treatment option.

Question 14. Should long-acting GLP-1 receptor agonists vs. sulfonylureas be used for adults with T2DM and DKD who have not achieved individualized glycemic targets despite using metformin and SGLT-2i?

Recommendation 14. *For adults with T2DM and DKD who have not reached their individualized glycemic targets despite using metformin and SGLT-2i, we suggest using long-acting GLP-1 receptor agonists over sulfonylureas (Conditional recommendation, very low certainty evidence).*

Rationale. Limited studies have estimated “the efficacy of GLP-1 receptor agonists” and sulfonylureas, prompting the panel members to develop recommendations based on the efficacy of each treatment alone and their experience. A retrospective study of 18567 patients with T2DM and DKD found that the use of “SGLT-2is or GLP-1 receptor agonists” was associated with a significantly reduced risk of

hypoglycemia compared with sulfonylureas (HR 0.30, [0.14 to 0.65]; very low certainty, Table S15).⁹⁰

A systematic review including high-certainty evidence studies indicated that sulfonylurea treatment is associated with a high risk of ventricular arrhythmias.⁹¹

The guideline panel demonstrated that adding a GLP-1 receptor agonist can enhance blood sugar management and may offer additional health benefits in patients with T2DM and DKD who have not achieved adequate glycemic control despite initial treatment (typically metformin) and “SGLT-2i” treatment.

The main recommendations for glucose-lowering agents in patients with DKD are listed in Table 4.

4. Evaluation and Risk Assessment of Diabetic Kidney Disease:

Question 15. Should cystatin C vs. creatinine be used to assess kidney function (GFR) in adults with T2DM and DKD?

Recommendation 15. *For adults with T2DM and DKD, we suggest using a creatinine-based eGFRcr over cystatin C (Conditional recommendation, moderate certainty evidence).*

Remarks. eGFRcr-cys is recommended in clinical situations when eGFR-cr is less accurate and GFR affects clinical decision-making.

Rationale. This recommendation was based on different studies that evaluated the diagnostic performance of cystatin C compared to serum creatinine among patients with DKD.^{92–95}

Certain studies suggested that cystatin C offers comparable diagnostic performance, with a sensitivity of 0.86 ([0.82 to 0.90; very low certainty, Table S16) and specificity of 0.89 ([0.85 to 0.92]; very low certainty, Table S16), a positive likelihood ratio of 7.59 ([5.66 to 10.19]; very low certainty, Table S16) and diagnostic odds ratio of 48.03 [30.64 to 75.29]; very low certainty, Table S16).⁹² Nevertheless, a systematic review has concluded that creatinine-based estimation was superior to cystatin C-based estimation.⁹⁶

Another study comparing the accuracy of cystatin C-based equations (eGFRcys) with eGFRcr in calculating eGFR showed that eGFRcr better predicted the CKD stage. The authors used the “Modification of Diet in Renal Disease (MDRD)” and CKD-EPI to develop eGFRcr and Tan-C equations to calculate eGFRcys. Accuracy within 30% was higher among CKD-EPI compared to MDRD and Tan-C equations (80.7% vs. 78.8% and 78.8%, respectively; low certainty, Table S16).⁹⁵

Furthermore, a real-world study confirmed these findings, showing that while eGFRcr methods may exhibit some bias (median difference 8.7, [0.89 to 0.94];

low certainty, [Table S16](#)), they offer acceptable accuracy (P30 68.8%, 95% 67.8% to 69.7%; low certainty, [Table S16](#)) and precision (Interquartile range [IQR] 18.6, [0.2 to 18.8]; low certainty, [Table S16](#)). However, the combined eGFRcr-cys method demonstrated the least bias (2.5, [2.2 to 2.7]; moderate certainty, [Table S16](#)), the highest accuracy (P30 86.4%, [85.7 to 87.1]; moderate certainty, [Table S16](#)), and the best precision (IQR 13.6, [-3.5 to 10.0]; moderate certainty, [Table S16](#)).⁹⁴

While eGFRcr and eGFRcys showed discrepancies in clinical practice, the combined eGFR using both markers (eGFRcr-cys) proved to be more accurate.^{94,97}

The panel suggests using creatinine for calculating eGFR due to it being more readily available, easier to use, and less expensive than cystatin. However, considering eGFR based on both creatinine and cystatin C is advisable in specific clinical situations where eGFR based on creatinine (eGFR-cr) may be less accurate and where the estimate impacts clinical decisions. This approach is consistent with that of the KDIGO guidelines.¹⁹

The guideline panel estimated that investigations are required to estimate cost-effectiveness when comparing

cystatin C with creatinine. The guideline panel appraised that acceptability to key stakeholders varies and warrants further investigation.

Question 16. Should estimated GFR compared to measured GFR be used for measuring disease progression in adults with T2DM and DKD?

Recommendation 16. *When measuring disease progression in adults with T2DM and DKD, we suggest using a validated GFR estimating equation over measured GFR (Conditional recommendation, very low certainty evidence).*

Rationale. A non-randomized observational study (n=50) evaluated three different methods for estimating GFR compared to measured GFR in patients with T2DM.⁹⁸ The CKD-EPI formula underestimated GFR (MD -13.1, [-23.1 to -3.06; very low certainty, [Table S17](#)), whereas the MDRD formula overestimated GFR (MD 14.8, [5.07 to 24.52; very low certainty, [Table S17](#)). The Cockcroft–Gault (CG) method showed the smallest difference from measured GFR (MD 1.5, [-8.01 to 11.1; very low certainty, [Table S17](#)).⁹⁸ However, the bias between the measured GFR versus CG showed no significant difference ($p>0.05$).⁹⁸

The guideline panel deemed that using eGFR would result in large savings. Finally, the guideline

Table 4 - Strength and level of evidence for the recommendations for glucose-lowering therapies in patients with DKD.

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
8. For adults with T2DM and DKD, we recommend using SGLT-2i over no SGLT-2i.	Strong	Moderate	100%
9. For adults with T2DM, DKD, and “an eGFR >20 mL/min per 1.73 m ² ,” we recommend using an SGLT-2i over sulfonylurea, regardless of glycemic control levels.	Strong	Moderate	100%
10. For adults with “T2DM and DKD who have not met their individualized glycemic targets,” we recommend using SGLT-2i over metformin. Remarks: If further glycemic control is necessary, consider combining it with metformin.	Strong	Moderate	100%
11. In adults with T2DM and DKD, we recommend using GLP-1 receptor agonists over not using them to slow chronic kidney disease progression, reduce albuminuria, and achieve glycemic control. Remarks: “GLP-1 receptor agonists” are preferred for “patients with an eGFR ≥25 mL/min” in those with obesity and individuals with heart failure and preserved ejection fraction.	Strong	Moderate	100%
12. For adults with T2DM and DKD, we suggest adding “GLP-1 receptor agonists to SGLT-2i for patients” who have not achieved the proteinuria target or glycemic control or those with increased cardiovascular risk	Conditional	Low	100%
13. For “adults with T2DM and DKD who have not achieved individualized glycemic targets despite using metformin and SGLT-2i,” we suggest using “long-acting GLP-1 receptor agonists” over “DPP-4 inhibitors”.	Conditional	Low	100%
14. For “adults with T2DM and DKD who have not reached their individualized glycemic targets despite using metformin and SGLT-2i,” we suggest using “long-acting GLP-1 receptor agonists” over “sulfonylureas.”	Conditional	Low	100%
DKD: Diabetic kidney disease, DPP-4: Dipeptidyl Peptidase-4, GLP-1: Glucagon-Like Peptide 1, SGLT-2i: Sodium-Glucose Co-Transporter 2 Inhibitors, T2DM: Type 2 diabetes mellitus			

panel estimated that eGFR is an acceptable and feasible option.

This recommendation is aligned with the KDIGO guidelines, which state that the mechanism for reviewing and selecting equations should be specific for each region. Moreover, they recommend collaboration between the National Kidney Society and laboratory physician organizations to identify the appropriate equation.¹⁹

Question 17. Should an externally validated risk equation vs isolated eGFR values be used for estimating the absolute risk of renal failure among adults with T2DM and DKD?

Recommendation 17. *To estimate the absolute risk of renal failure among adults with T2DM and DKD, we suggest using an externally validated risk equation over isolated eGFR values (Conditional recommendation, very low certainty evidence).*

Rationale. A retrospective non-randomized study (n=1641) evaluated the kidney failure risk equation (KFRE) compared to eGFR for measuring and predicting the time to kidney failure in patients with CKD. The KFRE demonstrated high discrimination (c statistic 0.862, [0.838 to 0.889; very low certainty, **Table S18**). Regarding KFRE-based predictions, the estimated median time to kidney failure was 42 months [IQR 21-72] for 20% risk, 24 months [IQR 12-42] for 40% risk, and 18 months [IQR 9-32] for 50% risk (very low certainty, **Table S18**). Regarding eGFR-based predictions, the estimated median time to kidney failure was 45 months [IQR 23-78] for “eGFR of 20 mL/min/1.73m²,” 23 months [IQR 11-39] for “eGFR of 15 mL/min/1.73m²,” and 11 months [IQR 5-18] for eGFR of 10 mL/min/1.73m² (very low certainty, **Table S18**).⁹⁹ However, the study design introduces a risk of bias, and the certainty of this evidence was considered very low. Furthermore, the study did not report on KFRE calibration, which is essential for accurate risk estimation.

While both KFRE and eGFR can be used in clinical practice, predictive frameworks designed to forecast kidney failure progression in patients with CKD demonstrate substantial precision and practical clinical utility. Patient-specific risk stratification tools strengthen therapeutic decision processes, enhance dialogue between clinicians and patients, and enable tailored treatment approaches for individuals with CKD.¹⁰⁰

Despite limited evidence, the guideline panel suggests that using an externally validated risk equation, such as KFRE, is generally more effective than relying solely on isolated eGFR values for estimating the absolute risk of

renal failure among adults with T2DM and DKD. This equation incorporates multiple variables, including age, sex, urine ACR (UACR), and eGFR, providing a more comprehensive assessment of renal failure risk. This approach has been externally validated and shown to improve prediction accuracy compared to using eGFR alone.

This recommendation aligns with other international guidelines, demonstrating that risk reporting in laboratories and electronic medical records should follow standardized formats with clear guidance on thresholds. Additionally, local validation before implementation is crucial to ensure accurate calibration of risk prediction models. Externally validated equations that rely on collected data should be prioritized, supporting health equity and advancing global health objectives.¹⁹

Question 18. Should kidney biopsy vs. no biopsy be used for adults with T2DM and DKD?

Recommendation 18. *For adults with T2DM and DKD with features suggestive of non-DKD, we suggest performing a kidney biopsy over no biopsy (Conditional recommendation, very low certainty evidence).*

Rationale. This recommendation is based on a prospective cohort study (n=280)¹⁰¹ of patients with biopsy indications. Indications for diagnostic evaluation in patients with DM encompass several concerning presentations: the combination of microalbuminuria with significant hematuria or unexplained kidney impairment; pronounced protein excretion (particularly when severe), with or without microscopic hematuria; and accelerated kidney function deterioration. Histopathological examination of kidney tissue samples in patients with diabetic nephropathy revealed an unexpectedly high frequency of concurrent renal pathologies beyond typical diabetic changes (RR 2.80, [2.07 to 3.80]; very low certainty, **Table S19**). The risk of hematoma after biopsy showed no significant difference (RR 0.78, [0.54 to 1.13]; very low certainty, **Table S19**). Therefore, the study considered renal biopsy safe in patients with T2DM.¹⁰¹

While the certainty is low, additional studies have highlighted the importance of distinguishing DKD from non-DKD in patients with T2DM to tailor treatment strategies.¹⁰² Notably, non-DKD is prevalent among patients with T2DM, with rates between 43.5–50%.^{103,104} Key predictors for non-DKD include a shorter DM duration, absence of diabetic retinopathy, higher red blood cell count in urine, and negative urinary glucose excretion.¹⁰⁵

A retrospective study emphasized that nephrotic-range proteinuria in patients with T2DM should encourage a kidney biopsy, particularly for those lacking

diabetic retinopathy, with a shorter DM duration, or with positive urinary sediment.¹⁰⁶

Considering the clinical necessity of distinguishing DKD from other kidney disorders in patients with T2DM who exhibit features suggestive of non-DKD, the guideline panel suggests performing a kidney biopsy for those patients. Our recommendation aligns with that of the KDIGO guidelines,¹⁹ which considers kidney biopsy a safe and effective diagnostic tool for identifying etiologies and guiding treatment when clinically indicated.

Question 19. Should spot urine protein/creatinine ratio vs 24-hour urine quantitative protein measurement in random urine samples be used for adults with T2DM and DKD?

Recommendation 19. For adults with T2DM and DKD, we suggest using either spot urine protein/creatinine ratio or 24-hour urine quantitative protein measurement in random urine samples (Conditional recommendation, very low certainty evidence).

Rationale. Our recommendation is based on a retrospective study (n=122) of Saudi patients with T2DM and diagnosed with DKD for at least one year.¹⁰⁷

The sensitivity and specificity of the random albumin-to-creatinine ratio (RACR) for various levels of albuminuria in patients with DM were assessed with varying cut-off values. The sensitivity and specificity were 1 and 0.913, respectively, for a cut-off range of 30–300 mg/g, whereas they were 1 and 0.941 for values exceeding 300 mg/g. These measures had very low certainty. Similarly, the positive predictive values (PPVs) for detecting albuminuria with these cut-off ranges were high (0.95 and 0.94 for the two ranges, respectively). In contrast, the negative predictive value (NPV) was 1 for both. The AUC was 0.999 for detecting micro-albuminuria and 0.982 for macro-albuminuria.¹⁰⁷ The study showed comparable test results, which were all based on very low-certainty evidence (Table S20).

A review¹⁰⁸ of 16 studies reported that RACR demonstrated 86% sensitivity and 60% specificity for screening microalbuminuria and 75% sensitivity and 99% specificity for screening macroalbuminuria in patients with T2DM.

Considering that both tests are acceptable and feasible with comparable efficacy, the guideline panel emphasized that either test is a suitable urine sample test. This provides clinicians with flexible, evidence-based recommendations to effectively monitor DKD, ensuring optimal patient care while accommodating individual needs and circumstances.

The panelists recognize that ACR is considered the standard care test for patients with DKD since it

effectively identifies microalbuminuria during the early stages. Moreover, they advise considering the protein/creatinine ratio as an alternative if ACR is unavailable.

Question 20. Should dipstick testing vs protein/creatinine ratio in random urine samples be used for the diagnosis of adults with T2DM and DKD?

Recommendation 20. For adults with T2DM, DKD, and albuminuria, we suggest against using dipstick testing over protein/creatinine ratio in random urine samples (Conditional recommendation, very low certainty evidence).

Rationale. Accurate assessment of albuminuria is crucial for diagnosing and managing CKD in patients with DM. Urine dipstick testing is commonly used; however, it lacks sensitivity for detecting early increases in protein excretion.¹⁰⁹ Our recommendation is based on a diagnostic test accuracy study,¹¹⁰ which included Japanese adult patients with “an eGFR of ≥ 15 mL/min/1.73 m²” and “a urine protein-to-creatinine ratio (uPCR) of <0.5 g/gCr” at baseline. The sum of three urine protein dipstick scores demonstrated a sensitivity of 0.532 and a specificity of 0.907 for predicting microalbuminuria. The PPV was 0.891, whereas the NPV was 0.576. The sensitivity for the sum of three uPCRs was higher than that of the urine protein dipstick (0.792), whereas specificity was comparable to that of the urine protein dipstick (0.889) (Table S21).

Similarly, a Korean study (n=20759) compared the urine dipstick test with urine ACR for detecting albuminuria in patients with CKD.¹¹¹ The study concluded that the dipstick test demonstrated poor sensitivity and high false-positive rates compared to ACR, supporting the use of uPCR for proteinuria detection.¹¹¹

Despite the low certainty of evidence, the guideline panel estimated that using uPCR in random urine samples offers a more reliable, feasible, accurate, and clinically actionable assessment of albuminuria compared to dipstick testing. Moreover, they advise considering the protein/creatinine ratio as an alternative if ACR is unavailable.

Question 21. Should estimated albumin excretion rate vs urine albumin-creatinine ratio be used in adults with T2DM and DKD to assess albuminuria?

Recommendation 21. For adults with T2DM, DKD, and albuminuria, we suggest against using the albumin excretion rate instead of the urine albumin-creatinine ratio (Conditional recommendation, low certainty evidence).

Rationale. This recommendation is based on a derivation and validation study,¹¹² which included data from three previous studies (MDRD, CRIC, and DCCT-EDIC studies).^{113–115} The recommendation is drawn from the DCCT, without direct evidence.

In the DCCT cohort, the sensitivity and specificity of detecting albuminuria >30 mg/24 h were 0.88 and 0.99, respectively, using the estimated albumin excretion rate and 0.64 and 1, respectively, using the albumin-creatinine ratio (Table S22).¹¹⁵

In contrast, the PREVEND Study aimed to determine whether calculating the estimated albumin excretion rate using spot ACR rate would improve albuminuria assessment accuracy compared to ACR alone, demonstrating that estimated albumin excretion was more accurate than ACR for assessing albuminuria.¹¹⁶ Additionally, using ACR as an alternative to 24-hour urinary albumin excretion for albuminuria assessment and classification has demonstrated strong concordance between the 2 methods.¹¹⁷

According to the KDIGO's practice recommendation, conducting repeat tests is advised in cases of a high urinary ACR, hematuria, or low eGFR to verify the presence of CKD.¹⁹

The guideline panel suggests using the albumin-creatinine ratio to assess albuminuria among patients with DKD, since it is a moderately priced and likely acceptable option for diagnosing and monitoring albuminuria in DKD. Moreover, it correlates well with disease progression and is deemed feasible, requiring only a single, random urine sample.

Question 22. Should an annual assessment of serum creatinine to determine eGFR and urine ACR vs other monitoring strategies starting five years after T2DM diagnosis be used to identify the stage and monitor the progression of DKD?

Recommendation 22. For adults with T2DM and DKD, we suggest an annual assessment using either serum creatinine to determine eGFR and urine ACR or other available proteinuria monitoring strategies (Conditional recommendation, very low certainty evidence).

Rationale. No evidence exists regarding the most appropriate method to monitor patients with DKD annually. This recommendation is based on the known benefits of frequent DKD monitoring and a retrospective study, which concluded that close serum creatinine level screening and regular follow-up should be considered alongside effective therapeutic interventions.¹¹⁸

A retrospective cohort study analyzed the medical records of 387 patients with DM over 5 years,¹¹⁸ demonstrating an increase in serum creatinine from baseline to one year (MD 0.07 mg/dL, [0.03 to 0.1]; very low certainty, Table S23). The change in serum creatinine from baseline to 2 years showed a similar pattern, with an MD of 0.08 mg/dL ([0.04 to 0.1]; very low certainty, Table S23). The MD in serum creatinine was 0.07 mg/dL at three years ([0.04 to 0.1]; very low

certainty, Table S23). Moreover, further increases in the MD of serum creatinine at 4 and 5 years were observed (MD 0.13 mg/dL, [0.09 to 0.2], and 0.15 mg/dL, [0.1 to 0.2], respectively; very low certainty, Table S23).

The incidence of serum creatinine doubling from baseline among patients with DM ≥ 5 years was notable (HR 27.01, [0.57 to 1274.10]; very low certainty, Table S23), and the mean survival time was 55.4 years ([54 to 56.8]; very low certainty, Table S23).¹¹⁸

Screening for CKD should be considered for all patients with T2DM using spot urine ACR and eGFR at diagnosis and at least annually thereafter. Moreover, early screening facilitates timely diagnosis of CKD, patient counseling, pharmacological treatment, and referral to a nephrologist when necessary.¹¹⁹

The guideline panel emphasizes the importance of annual screening of patients with DKD using available monitoring strategies.

The KDIGO guidelines recommend an annual assessment of patients with T2DM and DKD and GFR of > 60 ml/min/1.73 m² (CKD G1-G2), every 6 months for those with GFR of 30- 59 ml/min/1.73 m² (CKD G3), every 3 months for those with GFR of 15- 29 ml/min/1.73 m² (CKD G4), and every 6 weeks for those with GFR of <15 ml/min/1.73 m² (CKD G5), underlining that CKD symptoms may be obvious at the time of "T2DM diagnosis," and CKD 6 screening should begin at that point.¹⁹

A summary of the evaluation and risk assessment recommendations endorsed by the panel is shown in Table 5.

5. Comprehensive Management Approaches for Adults with DKD:

Question 23. Should an initial conservative approach using intensive medical therapy vs an initial invasive strategy be used for patients with T2DM, DKD, and ischemic heart disease?

Recommendation 23. For people with T2DM, DKD, and ischemic heart disease, we recommend using an initial conservative approach using intensive medical therapy over an initial invasive strategy (Strong recommendation, high certainty evidence).

Rationale. Our recommendation is in line with post hoc findings (n=2287) in patients with stable coronary artery disease and CKD in the United States and Canada. The research evaluated whether "percutaneous coronary intervention" plus "optimal medical therapy" provided superior outcomes compared to "optimal medical therapy alone" in reducing deaths and non-fatal myocardial infarctions among patients. The "optimal medical therapy" included antiplatelet therapy such as aspirin, clopidogrel, anti-ischemic therapy

Table 5 - Strength and level of evidence for the recommendations for evaluation and risk assessment of DKD.

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
8. For adults with T2DM and DKD, we suggest using a creatinine-based eGFR _{cr} over cystatin C. Remarks: eGFR _{cr} -cys is recommended in “clinical situations when eGFR-cr is less accurate and GFR affects clinical decision-making.”	Conditional	Moderate	91%
9. When measuring disease progression in “adults with T2DM and DKD,” we suggest using “a validated GFR estimating equation” over “measured GFR.”	Conditional	Very low	100%
10. To estimate “the absolute risk of renal failure” among adults with T2DM and DKD, we suggest using “an externally validated risk equation” over “isolated eGFR values.”	Conditional	Very low	100%
11. For adults with T2DM and DKD with features suggestive of non-DKD, we suggest performing a kidney biopsy over no biopsy.	Conditional	Very low	91%
12. For adults with T2DM and DKD, we suggest using either “spot urine protein/creatinine ratio” or “24-hour urine quantitative protein measurement” in random urine samples.	Conditional	Very low	100%
13. For adults with T2DM, DKD, and albuminuria, we suggest against using dipstick testing over protein/creatinine ratio in random urine samples.	Conditional	Very low	100%
14. For adults with T2DM, DKD, and albuminuria, we suggest against using the albumin excretion rate instead of the urine albumin-creatinine ratio.	Conditional	Low	100%
15. For adults with T2DM and DKD, we suggest an annual assessment using either serum creatinine to determine eGFR and urine ACR or other available proteinuria monitoring strategies	Conditional	Very low	100%

ACR: Albumin-Creatinine ratio, DKD: Diabetic kidney disease, eGFR: Estimated Glomerular Filtration Rate, GFR: Glomerular Filtration Rate, T2DM: Type 2 diabetes mellitus

such as long-acting metoprolol, and/or amlodipine, lisinopril or losartan, and long-acting nitrates, lipid-lowering therapy such as simvastatin, as well as lifestyle interventions.¹²⁰

The analysis revealed no significant difference in the rate of death, myocardial infarction, or new-onset heart failure between the 2 groups (HR 0.81, [0.44 to 1.46], HR 0.93, [0.54 to 1.57], and HR 0.64, [0.25 to 1.62], respectively; moderate certainty, [Table S24](#)).¹²⁰

Recent studies examined the effectiveness of invasive versus conservative strategies for managing stable coronary disease. The ISCHEMIA trial found no difference in cardiovascular outcomes or mortality between invasive and conservative approaches over 3.2 years in patients with stable coronary disease.¹²¹

The guideline panel suggests that a conservative approach, using intensive medical therapy, including antiplatelet, anti-ischemic, and lipid-lowering therapies as well as lifestyle interventions, may be appropriate for some patients, reserving invasive interventions such as angiography and revascularization for cases with clear indications. Additionally, the panel considers optimal medical therapy as an acceptable and feasible approach.

Our recommendations align with the KDIGO guidelines for medical treatment;¹⁹ however, they are

not applicable in individuals with severe angina, as these patients were excluded from the definitive trials.

Formally evaluating the cost-effectiveness of “intensive medical therapy” compared to “an initial invasive” approach is not feasible owing to the diverse results from research involving individuals with stable ischemic heart disease. Insufficient power to identify an effect on angina is one significant reason for the different results between the two trials. Moreover, factors such as CKD-mineral bone disease and coronary calcification in CKD, which increase the prevalence of microvascular disease and present additional difficulties in revascularization, may have contributed to these discrepancies.¹²²

Question 24: Should early initiation of dialysis vs late initiation (depending on the presence and severity of symptoms [fatigue, nausea, etc.] and blood test results [electrolytes, anemia markers]) be used in adults with T2DM and DKD?

Recommendation 24: For adults with T2DM and DKD, we suggest against early initiation of dialysis (Conditional recommendation, moderate certainty evidence).

Remarks. Late initiation of dialysis should depend on the presence and severity of symptoms and blood test results (electrolytes and anemia markers).

Rationale. This recommendation was based on an RCT (n=828) of patients who were assigned to initiate dialysis at an eGFR of 10.0–14.0 mL/min (early-start group) or to receive standard care until the GFR reached 5.0–7.0 mL/min (late-start group).¹²³

The follow-up duration of this RCT was 3.59 years. No significant difference was observed in the death rate between the early dialysis and standard dialysis groups (HR 1.04, [0.83 to 1.30]; low certainty, [Table S25](#)). Deaths after transplantation were comparable between the groups (HR 1.01, [0.81 to 1.26]; low certainty, [Table S25](#)). Similarly, the rate of a composite cardiovascular event (HR 1.23, [0.97 to 1.56]; low certainty, [Table S25](#)), “nonfatal myocardial infarction” (HR 1.39, [0.91 to 2.15]; low certainty, [Table S25](#)), and nonfatal stroke (HR 1.21, [0.73 to 2.00]; low certainty, [Table S25](#)) were comparable between the groups.¹²³

A non-significant difference was reported in cardiovascular deaths, hospitalization due to new-onset angina, and transient ischemic attacks between the early dialysis and standard dialysis groups (HR 0.94, [0.67 to 1.32]; HR 1.15, [0.75 to 1.78], and HR 2.36, [0.73 to 7.68], respectively; low certainty, [Table S25](#)).¹²³

Other complications included a need for access revisions or access-site infection (HR 1.08, [0.85 to 1.35], and HR 0.99, [0.67 to 1.48], respectively; low certainty, [Table S25](#)), which were similar between the groups.¹²³

Other manifestations, including serious fluid or electrolyte disorders and placement of a temporary dialysis catheter, were similar between the groups (HR 0.88, [0.71 to 1.10], and HR 1.03, [0.80 to 1.23], respectively; low certainty, [Table S25](#), respectively).¹²³

However, alternative evidence indicates that postponing dialysis initiation until it is clinically necessary may be advantageous, particularly for older patients, and that the choice to begin dialysis should be made collaboratively by the patient and healthcare provider.¹²⁴

The latest KDIGO guidelines advise initiating dialysis when one or more of the following conditions are present: signs of kidney failure or uncontrolled volume or blood pressure, nutritional decline, and cognitive impairment.¹⁹

While no difference was observed between early and late initiation of dialysis, the guideline panel suggests against “early initiation of dialysis” to avoid exposing patients to dialysis-related complications, including infections, vascular access problems, cardiovascular instability, and malnutrition. Additionally, they acknowledge that late initiation of dialysis should depend on symptom presence and severity, and blood test results.

The KDIGO guidelines recommend initiating “dialysis based on a composite assessment” of a patient’s symptoms, QoL, signs, preferences, GFR level, and laboratory abnormalities.¹⁹ Symptoms directly attributable to kidney failure—such as neurological manifestations from uremia, pericarditis, anorexia, refractory acid-base or electrolyte imbalances, intractable pruritus, and serositis—are clear indications for initiating dialysis. Critical considerations include challenges in managing fluid balance or blood pressure, progressive malnutrition that is unresponsive to dietary interventions, and cognitive decline. While the eGFR provides valuable information, it should not be the sole determinant for dialysis initiation. Recent studies suggest that initiating dialysis based solely on eGFR without accompanying symptoms may not confer additional benefits and may be associated with increased risks.

Question 25. Should the initiation of erythropoiesis-stimulating agents (ESAs) vs. no ESAs be used in adults with T2DM, DKD, and anemia?

Recommendation 25. For adults with T2DM, DKD, and anemia, we suggest using erythropoiesis-stimulating agents over no treatment (Conditional recommendation, moderate certainty evidence).

Rationale. The ESAs play a crucial role in CKD management by effectively controlling hemoglobin levels, reducing blood transfusion requirements, and improving patient QoL. ESAs have demonstrated potential benefits for kidney transplant recipients and may have cardioprotective effects.¹²⁵

This recommendation is based on a multicenter RCT (n=4038),¹²⁶ which included patients with DM, CKD, and anemia. In total, 2012 patients were assigned to receive darbepoetin alfa, targeting a hemoglobin level of ~13 g/dL, whereas 2026 received a placebo with rescue darbepoetin alfa if their hemoglobin dropped below 9.0 g/dL.¹²⁶

Initiation of darbepoetin alfa significantly improved hemoglobin levels compared to placebo after a 48-month follow-up. Median hemoglobin levels were higher in the darbepoetin alfa group than in the placebo group (12.5 g/dL, IQR 12.0–12.8; 10.6 g/dL, and IQR 9.9–11.3; $p<0.001$, respectively; moderate certainty, [Table S26](#)). The study found no significant effect of darbepoetin alfa on ESKD incidence or the composite outcome of death from any cause or a cardiovascular event (HR 1.02, [0.87 to 1.18; and HR 1.05, [0.94 to 1.17], respectively; high certainty, [Table S26](#)). However, darbepoetin alfa was associated with a higher risk of death from stroke (HR 1.92, [1.38 to 2.68]; high certainty, [Table S26](#)), with no significant impact on the risk of death from

myocardial infarction, heart failure, or cardiovascular causes. Adverse event profiles indicated a higher risk of venous (2.0% vs. 1.1%, $p=0.02$) and arterial (8.9% vs. 7.1%, $p=0.04$) thromboembolic events associated with darbepoetin alfa.¹²⁶

Cancer-related adverse events and mortality showed no significant differences between the groups. Red cell transfusion requirements were significantly reduced with darbepoetin alfa (HR 0.56, [0.49 to 0.65]; high certainty, [Table S26](#)). Diastolic blood pressure was higher in the darbepoetin alfa group (median DBP 73 mmHg vs. 71 mmHg, $p<0.001$; moderate certainty, [Table S26](#)). Moreover, initiation of darbepoetin alfa improved fatigue scores over 25 weeks (mean score increase of 4.2 ± 10.5 vs. 2.8 ± 10.3 , $p<0.001$; moderate certainty, [Table S26](#)). However, serious adverse events occurred at similar rates in both groups. Overall, ESAs demonstrated efficacy in increasing hemoglobin levels and reducing transfusion requirements; however, they were associated with increased risks of thromboembolic events and stroke.¹²⁶

Current clinical practice advises against administering disproportionately high ESA doses to achieve hemoglobin targets, particularly in patients with considerable cardiovascular morbidity or ESA resistance. Individualized treatment approaches are warranted to balance the benefits of reducing transfusions and anemia-related symptoms against potential risks.¹²⁵

The guideline panel suggests using ESAs among patients with T2DM, DKD, and anemia, recognizing their potential benefit in managing anemia and reducing transfusions and considering them a likely acceptable and feasible treatment option.

Question 26. Should early education at eGFR <15 mL/min and counseling on renal replacement therapy (RRT) options vs crash dialysis start be used in adults with T2DM and DKD?

Ungraded statement 1. For adults with T2DM and DKD with eGFR <15 mL/min, we strongly advise early education and counseling on RRT options over crash dialysis (Good practice statement).

Rationale. This recommendation is based on the experts' opinion owing to the lack of direct evidence. A non-randomized retrospective cohort study ($n=1218$) involving consecutive patients with pre-dialysis CKD over a follow-up period of 30 months used propensity score matching to pair 149 recipients and non-recipients. The outcomes were compared between those who received multidisciplinary pre-dialysis education and those who did not.¹²⁷

The study suggested that early education and counseling can reduce the risk of urgent unplanned

hemodialysis (HR 0.51, [0.27 to 0.97]). Pre-dialysis education reduced CVD risk, hospitalization rate, and number of hospitalization days spent (HR 0.243, [0.076 to 0.777]; (MD 1.5 - admissions per year, [-0.28 to -0.018]; MD -2.89 days, [-4.85 to -0.92], respectively). Moreover, the risk of infection was reduced, but the evidence's certainty was very low (HR 0.44, [0.17 to 1.11]). Furthermore, a slightly greater decline in eGFR was observed among pre-dialysis education recipients than non-recipients (median change of -0.16 mL/min per 1.73m^2 per month vs. -0.12 mL/min per 1.73m^2 per month).

Frequent visits can pose a challenge for patients with DKD; therefore, various educational methods require exploration. An RCT assessing the impact of comprehensive pre-dialysis education delivered via telemedicine for patients with CKD compared to a standard care group receiving face-to-face education indicated that nearly 90% of participants (telemedicine: 87%, face-to-face: 95%) were able to select a treatment option after receiving education.¹²⁸

The guideline panel favors early education and counseling on RRT for patients with T2DM and DKD with eGFR <15 mL/min, estimating it as moderately cost-saving and considering it a potentially acceptable and feasible option.¹²⁷

Question 27. Should close monitoring of kidney function and blood pressure throughout pregnancy with medication adjustments as needed vs. standard prenatal care be used in pregnant women with pre-existing T2DM and DKD?

Ungraded statement 2. For pregnant women with pre-existing T2DM and DKD, we strongly advise closely monitoring kidney function and blood pressure throughout pregnancy over standard prenatal care (Good practice statement).

Rationale. Limited studies have directly discussed the close monitoring of kidney function and blood pressure throughout pregnancy and standard prenatal care in pregnant women with pre-existing T2DM and DKD. Therefore, we developed our recommendation following the experts' experience and potential adverse events associated with DKD in pregnant women.

A systematic review of more than 15 studies and 843 pregnant women with DKD showed high rates of preeclampsia (up to 64%) and cesarean section (up to 100%). Maternal complications were more common, exhibiting more severe proteinuria and renal impairment.¹²⁹ Fetal outcomes included frequent occurrences of prematurity (up to 100%) and neonatal intensive care admissions (up to 75%). Additionally, fetal complications were more frequent, featuring more

severe proteinuria and renal impairment. Pregnancy can accelerate the progression of DKD, particularly among patients with CKD stages 3–5; therefore, pre-pregnancy counseling and close monitoring during pregnancy are essential.¹²⁹

In another meta-analysis, CKD during pregnancy was significantly associated with a higher risk of developing preeclampsia (adjusted OR 2.58, [1.33 to 5.01]), cesarean delivery (adjusted OR 1.65, [1.21 to 2.25]), babies who are small for gestational age (adjusted OR 1.93, [1.06 to 3.52]) and preterm births (adjusted OR 1.73, [1.31 to 2.27]).¹³⁰

Considering the high risk of complications associated with CKD during pregnancy, these patients should be closely monitored.^{130,131} Furthermore, CKD severity correlates with the likelihood of negative outcomes during pregnancy, necessitating a collaborative strategy for preconception guidance and pregnancy management for achieving the best outcomes for both patients with CKD and their babies.¹³²

Question 28. Should metabolic acidosis be treated vs. no treatment for slowing DKD progression?

Recommendation 26. For adults with T2DM and DKD, we suggest treating metabolic acidosis over no treatment (Conditional recommendation, moderate certainty evidence).

Rationale. Our recommendation aligns with two meta-analyses examining the effect of treating metabolic acidosis with sodium bicarbonate in patients with CKD.^{133,134} The first meta-analysis included 14 clinical trials with 1394 participants with CKD stages 3–5 and metabolic acidosis (<22 mEq/L) or low-normal serum bicarbonate levels (22–24 mEq/L).¹³³ The other meta-analysis included 14 RCTs evaluating the effect of sodium bicarbonate in 2037 patients with CKD and metabolic acidosis.¹³⁴ Addition of sodium bicarbonate improved kidney function, as reflected by a slower eGFR decline (MD -3.3 mL/min per 1.73 m², [-4.4 to -2.1]; very low certainty, Table S27). Similarly, a lower eGFR decline per year was observed in the group treated with sodium bicarbonate compared to the no-treatment group (MD -2.1 mL/min per 1.73 m², [-2.8 to -1.4]; low certainty, Table S27). Additionally, a significant decrease was observed in the progression to ESKD (RR 0.3, [0.2 to 0.6]; very low certainty, Table S27) and UACR (MD -52 mg/g, [-76 to -27]; very low certainty, Table S27).¹³³

In the other meta-analysis, several benefits of metabolic acidosis treatment were reported, including improved eGFR (Standardized mean difference [SMD] 0.33, [0.03 to 0.63]; very low certainty, Table S27) and a lower rate of hospitalization (OR 0.37, [0.25 to 0.55];

moderate certainty, Table S27) compared to the control group. However, some concerns emerged, such as an increase in the systolic blood pressure compared to that in controls (SMD 0.1, [0.01 to 0.2]; moderate certainty, Table S27). Moreover, the rate of all-cause mortality did not significantly differ between the groups (OR 0.72, [0.40 to 1.31]; very low certainty, Table S27).¹³⁴

Based on the evidence, the guideline panel considers that treating metabolic acidosis is likely to be an acceptable and feasible treatment method for DKD.

While KDIGO had not issued a graded recommendation on this issue owing to limited high-quality RCTs,¹⁷ they recommend monitoring treatment to maintain bicarbonate levels within the normal range and prevent adverse effects on blood pressure, potassium levels, and fluid status.¹⁷

Question 29. Should intravascular contrast agents vs. other imaging modalities be used in adults with T2DM, DKD, and coronary artery disease?

Recommendation 27. For adults with T2DM and DKD with acute coronary syndrome requiring intervention, we recommend using intravascular contrast agents over other imaging modalities (Strong recommendation, moderate certainty evidence).

Rationale. The current recommendation is based on indirect evidence of a meta-analysis with 20 RCTs involving 11698 adults with coronary artery disease.¹³⁵

In the analysis of 13 RCTs, the risk of cardiac deaths was lower in patients receiving intravascular contrast agents than those using other imaging modalities (Rate ratio 0.53, [0.39 to 0.72]; moderate certainty, Table S28). The risk of myocardial infarction was lower among patients treated with intravascular contrast agents in 17 RCTs (Rate ratio 0.81, [0.68 to 0.97]; moderate certainty, Table S28).

Stent thrombosis was less common among patients treated with intravascular contrast agents in 12 RCTs (Rate ratio 0.44, [0.27 to 0.72]; moderate certainty, Table S28). Similarly, the risk of target vessel revascularization was lower in patients treated with intravascular contrast agents (Rate ratio 0.74, [0.61 to 0.89]; moderate certainty, Table S28). The risk of target lesion revascularization was reduced among patients receiving intravascular contrast agents in 14 RCTs (Rate ratio 0.71, [0.59 to 0.86]; moderate certainty, Table S28). The all-cause mortality rate was lower in the intravascular contrast agent group, although the difference was non-significant (rate ratio 0.81, [0.64 to 1.02], moderate certainty, Table S28).

While intravascular contrast has benefits, it presents several risks. Extended procedural duration, higher contrast dosage, and increased radiation exposure have

been associated with peri-procedural complications, including early mortality and the need for emergency interventions.¹³⁶

Given the demonstrated benefits of intravascular contrast agents in improving diagnostic precision and facilitating urgent clinical interventions, along with their practical applicability and an acceptable safety profile, the overall benefit-to-risk ratio clearly favors their use in patients with DKD. Despite the moderate certainty of the supporting evidence, these advantages provide a strong rationale for issuing a strong recommendation in favor of intravascular contrast agents over alternative imaging modalities.

Question 30. Should optimal blood pressure control vs. less intensive blood pressure control be used for reducing the risks of developing and progressing DKD and CVD among adults with T2DM and DKD?

Recommendation 28. For adults with T2DM and DKD, we suggest using either optimal (SBP of <120 mmHg) or less intensive (SBP of <130 mmHg) blood pressure control (Conditional recommendation, low certainty evidence).

Rationale. This recommendation is based on a post-hoc analysis of 2 RCTs involving 341 adult patients with DKD. Participants were assigned to either a standard blood pressure control strategy or a strict blood pressure control strategy.¹³⁷

No significant difference was found in the proportions of patients who achieved a reduction in cardiovascular/renal events (follow-up: 24 weeks) (HR 1.32, [0.60 to 2.92]; low certainty, [Table S29](#)). Similar findings were observed for the reduction in cardiovascular outcomes at 24 weeks with strict blood pressure control (HR 2.08, [0.38 to 11.37]; very low certainty, [Table S29](#)). Regarding renal outcomes (composite of $\geq 50\%$ decline in eGFR or initiation of kidney replacement therapy) at 24 weeks, no significant difference was noted between the two groups (HR 1.15, [0.47 to 2.84]; very low certainty, [Table S29](#)). In addition, the risk of adverse events (composite of orthostatic hypotension, bradycardia, syncope, acute kidney injury, or electrolyte imbalance) at 24 weeks did not significantly differ between the two blood pressure control strategies (RR 1.09, [0.85 to 1.40]; low certainty, [Table S29](#)).¹³⁷

The guideline panel suggests using optimal (SBP of <120 mmHg) or less intensive (SBP of <130 mmHg) blood pressure control, acknowledging the variability in individual patient responses and the need for a personalized approach to balance benefits with potential risks. Regarding KDIGO practice guidelines, they recommend a target systolic blood pressure of <120 mmHg for patients with CKD.^{19,138}

However, they estimated that frail individuals who have a “limited life expectancy” or have “a history of falls and fractures” may face a higher risk of adverse events with the pursuit of blood pressure targets below 120 mmHg. Postural hypotension in such individuals is linked to negative outcomes. Therefore, carefully balancing the benefits of slowing eGFR decline against the potentially life-altering consequences of falls, fractures, and related events is crucial when selecting specific blood pressure targets.^{19,138} Moreover, the KDIGO practice guidelines align with our guideline panel’s perspective and acknowledge individualized blood pressure targets and use of agents according to age, risk of CKD progression, treatment tolerance, CVD, and other comorbidities.^{19,138,139}

Question 31. Should optimal lipid control vs. standard lipid control be used for reducing the risks of developing and progressing DKD and CVD among adults with T2DM and DKD?

Recommendation 29. For adults with T2DM and DKD, we suggest optimal lipid control over standard lipid control (Conditional recommendation, very low certainty evidence).

Rationale. Our recommendation is based on a meta-analysis of nine studies, including 3,426 patients receiving five different statins, that assessed the impact of statins on the management of early diabetic nephropathy.¹⁴⁰

The intervention group in the RCTs showed a significant improvement in eGFR and serum creatinine (MD 5.8, [2.21 to 9.4], $p=0.002$; low certainty; MD -0.46, [-0.69 to -0.24], $p<0.0001$; low certainty, [Table S30](#)). Cholesterol and triglyceride levels were lower in the intervention group than in the control group (MD -54.09, [-68.02 to -40.16], $p<0.00001$; very low certainty; MD -42.19, [-55.54 to -28.84], $p<0.00001$; very low certainty, [Table S30](#)). Additionally, improvement in high-sensitivity C-reactive protein was lower in the intervention group (MD -1.2, [-2.05 to -0.36], $p=0.005$; low certainty, [Table S30](#)).¹⁴⁰

The ESC/EAS guidelines estimated that the optimal lipid control targets depend on the patient’s cardiovascular risk level. The upper target level of plasma LDL-C concentration is set at 3.0 mmol/L (116 mg/dL) for individuals with low cardiovascular risk (SCORE <1%),¹⁴¹ whereas the target is 2.6 mmol/L (100 mg/dL) for those at moderate risk (SCORE 1–5% or younger patients with specific conditions). High-risk patients (SCORE >5% and <10% or with significant risk factors such as moderately elevated cholesterol, hypertension, or moderate CKD) should aim for LDL-C levels below 1.8 mmol/L (70 mg/dL). Very high-risk patients,

including those with a SCORE $\geq 10\%$, atherosclerotic cardiovascular disease, severe CKD, or DM with target organ damage, have a stricter target of 1.4 mmol/L (55 mg/dL).¹⁴¹

The KDIGO guidelines recommend assessing lipid profiles (total cholesterol, LDL-C, high-density cholesterol (HDL-C), and triglycerides) in patients with newly diagnosed CKD. However, they indicate that there is no requirement for lipid measurement follow-up for most patients (19). In addition, they acknowledge the benefits of LDL-C reduction using statin-based therapies in individuals with and without CKD.¹⁹ Treatment with statins is recommended for adults aged ≥ 50 years with CKD and eGFR ≥ 60 ml/min per 1.73 m² (including patients on dialysis) or for those aged 18–49 years with CKD and DM not treated with chronic dialysis or kidney transplantation. While statins or a combination of statin/ezetimibe is suggested for adults ≥ 50 years, eGFR <60 ml/min per 1.73 m², and not treated with chronic dialysis or kidney transplantation.¹⁹

The guideline panel deems optimal lipid control, estimated by the ESC/EAS working group, to be an acceptable and feasible option. However, this recommendation is conditional owing to the very low

certainty of the evidence, warranting further larger and higher-quality trials.

The key recommendations and statements issued by the panel to provide comprehensive management of patients with DKD are illustrated in **Table 6**.

6. Pharmacologic Interventions for Adults with DKD:

Question 32. Should RAAS inhibitors (ACEIs or ARBs) vs calcium channel blockers (CCBs) be used for decreasing disease progression in patients with T2DM, DKD, and severely increased albuminuria?

Recommendation 30. For adults with T2DM, DKD, and severely increased albuminuria (ACR >300 mg/day), we recommend using RAAS inhibitors (ACEIs or ARBs) over CCBs (Strong recommendation, moderate certainty evidence).

Remarks. ACEIs /ARBs should be titrated to the maximally tolerated/highest approved dose to achieve benefits. The current statement may imply administering the highest dose at treatment initiation.

Rationale. This recommendation is based on a meta-analysis of 23 RCTs (n=1805) that compared RAAS inhibitors to CCBs among patients with T2DM and DKD. RAAS inhibitors showed a more significant reduction in albuminuria than CCBs (SMD -0.442,

Table 6 - Strength and level of evidence for the recommendations for comprehensive management approaches for adults with DKD:

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
8. For patients with T2DM, DKD, and ischemic heart disease, we recommend using an initial conservative approach using intensive medical therapy over an initial invasive strategy.	Strong	High	100%
9. For adults with T2DM and DKD, we suggest against early initiation of dialysis. Remarks: Late initiation of dialysis should depend on the presence and severity of symptoms and blood test results (electrolytes and anemia markers).	Conditional	Moderate	100%
10. For adults with T2DM, DKD, and anemia, we suggest using erythropoiesis-stimulating agents over no treatment.	Conditional	Moderate	100%
11. For adults with T2DM and DKD, we suggest treating metabolic acidosis over no treatment.	Conditional	Moderate	100%
12. For adults with T2DM and DKD with acute coronary syndrome requiring intervention, we recommend using intravascular contrast agents over other imaging modalities.	Strong	Moderate	100%
13. For adults with T2DM and DKD, we suggest using either optimal (SBP of <120 mmHg) or less intensive (SBP of <130 mmHg) blood pressure control	Conditional	Low	100%
14. For adults with T2DM and DKD, we suggest optimal lipid control over standard lipid control.	Conditional	Very low	91%
Ungraded statement 1: For adults with T2DM and DKD with eGFR <15 mL/min, we strongly advise early education and counseling on RRT options over crash dialysis.	Good practice statement		100%
Ungraded statement 2: For pregnant women with pre-existing T2DM and DKD, we strongly advise close monitoring of kidney function and blood pressure throughout pregnancy over standard prenatal care.	Good practice statement		100%

DKD: Diabetic kidney disease, eGFR: Estimated glomerular filtration rate, RRT: Renal replacement therapy, T2DM: Type 2 diabetes mellitus

[-0.66 to -0.22]; moderate certainty, [Table S31](#)).¹⁴²

Further analyses of patients with severe albuminuria demonstrated comparable albuminuria-reducing effects between CCBs and ARB/ACEI.¹⁴² This observation is supported by a comprehensive meta-analysis of 19 RCTs,¹⁴³ which demonstrated that ACEI/ARB therapy showed no superior efficacy over alternative antihypertensive agents regarding cardiovascular and renal outcomes in patients with hypertension and DM without albuminuria.¹⁴³ Another recent meta-analysis of patients with DM and hypertension emphasized that RAAS inhibitors are superior to CCB regarding albuminuria reduction.¹⁴⁴

Kidney disease progression is characterized by proteinuria and declining renal function. The RAAS is a critical regulator of blood pressure, fluid volume, and sodium homeostasis. Research has established that RAAS hyperactivity significantly contributes to CKD progression.¹⁴⁵ Multiple experimental and clinical investigations have demonstrated that RAAS inhibition effectively reduces proteinuria, prevents kidney fibrosis, and slows the deterioration of renal function, offering nephroprotection across the spectrum of kidney disease severity.¹⁴⁵

The conflicting results in the literature regarding the efficacy of ACEIs /ARBs versus CCBs in patients with T2DM and DKD can be attributed to variations in study populations, endpoints, and disease severity. However, the guideline panel recommends that ACEIs/ARBs be titrated to the maximally tolerated or highest approved dose for adults with T2DM, DKD, and severely increased albuminuria (ACR >300 mg/day) to achieve benefits. The current statement may imply administering the highest dose at the initiation of treatment.

This reflects the panel's assessment favoring the intervention and suggests that RAAS inhibitors are likely to be acceptable and feasible. Similarly, international guidelines recommend RAAS inhibitors at the maximum tolerated dose.⁴⁶

Question 33. Should an ACEIs and ARBs combination vs. CCBs be used for decreasing disease progression in patients with T2DM, DKD, and severely increased albuminuria?

Recommendation 31. *For adults with T2DM, DKD, and severely increased albuminuria, we recommend against using any combination of ACEI and ARB (Strong recommendation, moderate certainty evidence).*

Rationale. This recommendation is based on two distinct RCTs owing to the absence of direct evidence comparing the combination of ACEIs and ARBs with CCBs. A comprehensive analysis comparing CCBs

with placebo among patients with DKD (N=1715) over a mean follow-up duration of 2.6 years revealed no significant differences between CCBs and placebo regarding the risk of developing serum creatinine doubling (RR 1.06, [0.84 to 1.35]; moderate certainty, [Table S32](#)), ESKD (RR 1.00, [0.76 to 1.32]; moderate certainty, [Table S32](#)), death from any cause (RR 0.88, [0.66 to 1.19], moderate certainty, [Table S32](#)), composite cardiovascular outcomes (RR 0.88, [0.69 to 1.12]; moderate certainty, [Table S32](#)), adverse events (RR 1.50, [0.25 to 8.97]; low certainty, [Table S32](#)), and composite renal outcomes (RR 1.04, [0.86 to 1.25]; moderate certainty, [Table S32](#)).¹⁴⁶

Another RCT comparing combination therapy (ACEI+ARB) with monotherapy concluded that ACEI and ARB combination therapy was associated with an elevated risk of adverse events in individuals with diabetic nephropathy.¹⁴⁷ The study found a non-significant higher risk of death (HR 1.04, [0.73 to 1.49]; moderate certainty, [Table S32](#)), myocardial infarction (HR 1.30, [0.87 to 1.97]; moderate certainty, [Table S32](#)), and serious adverse events (HR 1.09, [0.90 to 1.20]; moderate certainty, [Table S32](#)) with combination therapy compared to monotherapy.¹⁴⁷ Furthermore, an increased risk of hyperkalemia was detected among those receiving combination therapy than those receiving monotherapy (6.3 vs. 2.6 events/100 person-years; $p<0.001$). Similarly, a higher risk of acute kidney injury was observed with combination therapy (12.2 vs. 6.7 events/100 person-years, $p<0.001$).¹⁴⁷ This RCT was stopped owing to safety concerns from the increased odds of serious adverse events in the combination group compared to the monotherapy group.

A previous meta-analysis showed a significantly higher risk of developing hypotension (RR 2.21, [1.21 to 4.06] and cough (RR 4.55, [2.26 to 9.17] with combination therapy (ACEI+ARB) compared to monotherapy.¹⁴⁸

The panel regards the combination of ACEI and ARB as potentially unacceptable and associated with significant adverse events, which aligns with the KDIGO guidelines that recommend avoiding any combination therapy of ACEI and ARB in those with CKD with or without DM.¹⁹

Question 34. Should nonsteroidal mineralocorticoid receptor antagonists (MRAs) vs. no treatment be used in adults with T2DM and DKD?

Recommendation 32. *For adults with T2DM and DKD with a serum potassium level ≤ 5 mEq/L and an eGFR ≥ 25 mL/min/1.73 m², we recommend treatment with a nonsteroidal selective MRAs (Strong recommendation, moderate certainty evidence).*

Rationale. The recommendation is informed by a meta-analysis of seven RCTs involving 13,783 patients with DKD that compared nonsteroidal MRA treatment to control (patients either receiving placebo or any other medication for DKD).¹⁴⁹ The nonsteroidal MRAs resulted in a significant reduction in UACR at 90 days (MD -23.82, [-24.87 to -22.7]; moderate certainty, [Table S33](#)), chance of >57% decline in UACR (OR 0.70, [0.60 to 0.82]; high certainty, [Table S33](#)), and chance of 40% decline in GFR (OR 0.83, [0.75 to 0.92]; high certainty, [Table S33](#)).¹⁴⁹

Additionally, the nonsteroidal MRA treatment was associated with a lower risk of composite cardiac outcomes (OR 0.86, [0.78 to 0.95]; high certainty, [Table S33](#)), hospitalization for heart failure (OR 0.78, [0.66 to 0.92]; high certainty, [Table S33](#)), total adverse events (OR 0.97, [0.88 to 1.07]; high certainty, [Table S33](#)), and severe adverse events (OR 0.91, [0.84 to 0.97]; high certainty, [Table S33](#)). The risk of all-cause death (OR 0.89, [0.79 to 1.00]; high certainty, [Table S33](#)), hospitalization for any cause (OR 0.94, [0.88 to 1.01]; moderate certainty, [Table S33](#)), and progression to ESKD (OR 0.79, [0.62 to 1.01]; moderate certainty, [Table S33](#)) was lower in the nonsteroidal MRA treatment compared to controls.¹⁴⁹

An improvement in the systolic blood pressure at two years (MD -2.49 mmHg, [-2.98 to -2]; moderate certainty, [Table S33](#)), systolic blood pressure at four years (MD -1.57 mmHg, [-3.34 to 0.21]; low certainty, [Table S33](#)), and body weight at 2 years (MD 0.01 kg lower, [1.01 lower to 0.99 higher]; low certainty, [Table S33](#)) was observed with nonsteroidal MRA treatment.⁴³ In addition, nonsteroidal MRA treatment significantly decreased the occurrence of new-onset atrial fibrillation (OR 0.70, [0.52 to 0.93, $p=0.01$]).¹⁵⁰

However, no improvement was observed in HbA1c at 2 years (MD 0.02%, [0.05 to 0.08]; low certainty, [Table S33](#)), HbA1c at four years (MD 0.11%, [-0.01 to 0.23]; low certainty, [Table S33](#)), and body weight at four years (MD 0.33 kg, [-1.13 to 1.78]; low certainty, [Table S33](#)).¹⁴⁹ Moreover, nonsteroidal MRA treatment was associated with an increased risk of hyperkalemia (OR 2.19, [1.94 to 2.48]; high certainty, [Table S33](#)).¹⁴⁹ The expert panel determined that non-steroidal MRAs offer optimal benefit for T2DM patients experiencing cardiovascular complications and persistent albuminuria despite standard therapeutic interventions, based on comprehensive evidence evaluation. These medications demonstrate particular efficacy in addressing concurrent conditions, including cardiac insufficiency, excessive aldosterone production, and treatment-resistant high blood pressure. However, clinicians must remain vigilant

for potential adverse effects, notably elevated potassium levels and transient GFR reductions, particularly in patients with already compromised kidney function. Considering this benefit-risk profile, the panel strongly endorses this therapeutic class, specifically for patients with DKD maintaining serum potassium concentrations at or below 5 mEq/L and eGFR of at least 25 mL/min/1.73 m². The panel concluded that this intervention is cost-effective, acceptable, and likely to improve equity and feasibility in clinical practice. This recommendation is similar to that in the updated KDIGO guidelines (2024).¹⁹

Question 35. Should xanthine oxidase inhibitors vs no treatment be used for slowing DKD progression among adults with T2DM, DKD, and hyperuricemia?

Recommendation 33. *For slowing DKD progression among adults with T2DM, DKD, and hyperuricemia, we suggest against using xanthine oxidase inhibitors (Conditional recommendation, moderate certainty evidence).*

Rationale. This recommendation is supported by an RCT (n=86) comparing xanthine oxidase inhibitors to placebo in patients with T2DM, DKD, and serum uric acid levels from 4–10 mg/dL.¹⁵¹ Xanthine oxidase inhibitors showed a significant reduction in UACR (MD -0.43 mg/g, [-0.82 to -0.04]; moderate certainty, [Table S34](#)) and eGFR (MD -3.45 mL/min/1.73 m², [-4.00 to -2.89]; low certainty, [Table S34](#)). No significant difference was observed between xanthine oxidase inhibitors and placebo regarding the proportion of patients with >30% UACR reduction (RR 1.80, [0.96 to 3.43]; moderate certainty, [Table S34](#)), risk of total adverse events (RR 0.85, [0.52 to 1.40]; moderate certainty, [Table S34](#)), and drug-related serious adverse events (RR 0.320, [0.013 to 7.60]; low certainty, [Table S34](#)).¹⁵¹ Moreover, xanthine oxidase inhibitors were associated with decreased serum uric acid levels at week 12 (MD -3.18 mg/dL, [-3.07 to -3.28]; moderate certainty, [Table S34](#)). However, they were associated with drug-related adverse events (RR 2.86, [0.61 to 13.40]; moderate certainty, [Table S34](#)).¹⁵¹ This study had certain limitations that may influence the generalizability of its findings. The study was specifically designed to evaluate early changes in albuminuria over three months, which may have been insufficient to detect significant improvements in eGFR.

While certain RCTs have suggested potential reno-protective effects of xanthine oxidase inhibitors in patients with DKD, current evidence remains insufficient to recommend their use specifically for slowing CKD progression. However, in alignment with KDIGO guidelines, the panel suggests xanthine

oxidase inhibitors over uricosuric agents for treating symptomatic hyperuricemia in patients with CKD, although careful monitoring is warranted owing to the risk of drug-related serious adverse events.¹⁹

Question 36. Should Icosapent Ethyl vs. no treatment be used for adults with T2DM and DKD?

Recommendation 34. For adults with T2DM, DKD, and unachieved triglyceride targets (≤ 150 mg/dL) with statin maximum tolerated doses, we suggest using Icosapent Ethyl over no treatment (Conditional recommendation, moderate certainty evidence).

Rationale. No studies have assessed the efficacy of icosapent ethyl in patients with T2DM and DKD. Therefore, this recommendation is based on a multicenter RCT (n=8179) that compared icosapent ethyl to placebo among adult patients with elevated triglycerides receiving statins.¹⁵² Icosapent ethyl reduced composite cardiovascular outcomes (HR 0.75, [0.68 to 0.83]; moderate certainty, Table S35), cardiovascular death/myocardial infarction/stroke incidence (HR 0.74, [0.65 to 0.83]; moderate certainty, Table S35), cardiovascular death/myocardial infarction incidence (HR 0.75, [0.66 to 0.86]; moderate certainty, Table S35), fatal/nonfatal myocardial infarction risk (HR 0.69, [0.58 to 0.81]; moderate certainty, Table S35), and revascularization risk (HR 0.65, [0.55 to 0.78]; moderate certainty, Table S35). However, it increased the risk of atrial fibrillation/flutter (HR 1.50, [1.14 to 1.98]; moderate certainty, Table S35), bleeding (HR 1.20, [1.05 to 1.37]; moderate certainty, Table S35), and serious bleeding (HR 1.28, [0.98 to 1.67]; low certainty, Table S35).¹⁵²

The REDUCE-IT trial concluded that icosapent ethyl was a safe and effective therapeutic option for reducing triglyceride levels and the risk of ischemic events among patients with high triglyceride levels despite statin therapy, among patients with established cardiovascular disease or with diabetes.¹⁵³ Similar outcomes were observed across the broad range of baseline eGFR categories.¹⁵⁴ The guideline panel considers that icosapent ethyl is likely to be feasible and acceptable. The KDIGO guidelines recommend icosapent ethyl as an additional therapy for patients with DKD based on atherosclerotic cardiovascular disease risk and lipid levels.

Question 37. Should proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors vs. no treatment be used for adults with T2DM and DKD?

Recommendation 35. For adults with T2DM, DKD, and unachieved LDL-C targets with statin maximum tolerated doses, we suggest using PCSK9 inhibitors over no treatment (Conditional recommendation, moderate certainty evidence).

Rationale. This recommendation is based on an RCT (n=19477) comparing PCSK9 inhibitors to placebo among patients with CKD. PCSK 9 inhibitors reduced the risk of cardiovascular death/myocardial infarction/stroke (HR 0.79, [0.65 to 0.95]; moderate certainty, Table S36), and myocardial infarction (HR 0.70, [0.55 to 0.91]; moderate certainty, Table S36) in patients with CKD stage ≥ 3 . However, no significant change was observed in cardiovascular composite outcomes (HR 0.89, [0.76 to 1.05]; low certainty, Table S36).

Similar benefits were observed for cardiovascular composite outcomes (HR 0.85, [0.77 to 0.94]; moderate certainty, Table S36), cardiovascular death/myocardial infarction/stroke (HR 0.82, [0.72 to 0.93]; moderate certainty, Table S36), and myocardial infarction (HR 0.78, [0.66 to 0.91]; moderate certainty, Table S36) in patients with CKD stage 2. No significant differences were observed in adverse events between the groups in either CKD stage (RR 1.01, [0.98 to 1.04] for Stage ≥ 3 ; RR 1.00, [0.98 to 1.02] for Stage 2; moderate certainty, Table S36).¹⁵⁵ PCSK9 levels may mitigate CKD progression in patients with T2DM by positively influencing renal function impairment.¹⁵⁶ These results align with a previous meta-analysis showing that PCSK9 inhibitors are significantly associated with lower incidence of MI and cerebrovascular conditions, consistent with observed benefits in patients with CKD.¹⁵⁷

This recommendation is similar to that in the KDIGO guidelines, which recommends considering PCSK9 inhibitors for patients with CKD who meet the criteria for their use, as these inhibitors have demonstrated safe and effective reduction of atherosclerotic CVD risk when added to maximally tolerated statin-based treatments for high-risk patients. Current cardiology recommendations recommend using PCSK9 inhibitors as a supplementary treatment alongside dietary modifications and the highest tolerable dose of statin medication. This combination approach is indicated for two key patient populations: adults diagnosed with heterozygous familial hypercholesterolemia and individuals who have documented atherosclerotic cardiovascular disease but require further reduction in their LDL cholesterol levels beyond what statins alone can achieve.¹⁹

The guideline panel expressed that the balance between desirable and undesirable effects favors PCSK9 inhibitors. Additionally, using PCSK9 inhibitors would result in moderate savings. The guideline panel considers that PCSK9 inhibitors are likely to be acceptable and feasible for patients with DKD.

Question 38. Should statins vs. statin/ezetimibe combination be used for adults with T2DM and DKD?

Recommendation 36. *For patients with DKD who require lipid-lowering treatment, we suggest using either a Statin or a Statin/ Ezetimibe combination (Conditional recommendation, moderate certainty evidence).*

Remarks. A statin/ Ezetimibe combination is recommended if a higher statin dose is not tolerated or the target lipid level is not achieved.

Rationale. This recommendation was established in the IMPROVE-IT trial (n=18015), which compared statin/ezetimibe combination with statins alone among patients with cardiovascular disorders and creatinine clearance >30 mL/min.¹⁵⁸ The combination therapy reduced cardiovascular death/major coronary events/stroke in the overall population (HR 0.94, [0.89 to 0.99]; moderate certainty, [Table S37](#)), with more substantial effects among those with eGFR=45 (HR 0.87, [0.78 to 0.98]; moderate certainty, [Table S37](#)), eGFR=60 (HR 0.88, [0.82 to 0.95]; moderate certainty, [Table S37](#)), and eGFR=75 (HR 0.91, [0.84 to 0.99]; moderate certainty, [Table S37](#)). Combination therapy exhibited a lower risk for all-cause mortality than monotherapy (HR 0.95, [0.90 to 1.00]; moderate certainty, [Table S37](#)) within the overall population. Subgroup analysis revealed a greater reduction among patients with lower eGFR values: eGFR=45 (HR 0.90, [0.82 to 0.99]; moderate certainty, [Table S37](#)), eGFR=60 (HR 0.92, [0.86 to 0.98]; moderate certainty, [Table S37](#)), and eGFR=75 (HR 0.95, [0.88 to 1.02]; low certainty, [Table S37](#)).¹⁵⁸ Moreover, combination therapy demonstrated consistent lipid profile improvements across different kidney function categories. The absolute mean reduction for LDL-C ranged from 16.1 to 17.7 across different eGFR groups. HDL-C showed modest increases, with the most pronounced improvement being the MD from baseline to year 1 (standard deviation [SD] of 8.2 [9.9]) among patients with eGFR <45 mL/min/1.73m². Triglyceride reduction was notably more significant in the combination therapy group, with mean changes ranging from -21.1 to -21.8 across eGFR categories compared to minimal changes in the monotherapy group.¹⁵⁸ While this analysis did not specifically focus on patients with DKD, it provides valuable insights.

Additional clinical investigations have demonstrated that statin monotherapy significantly decreases cardiovascular incidents and overall mortality among individuals with chronic kidney disease, with particularly pronounced benefits observed in patients exhibiting either reduced kidney function (eGFR <60 mL/min) or increased urinary albumin excretion.^{159,160} The decision

to use a combination therapy depends on individual patient factors, such as tolerance of higher statin doses and achieving targeted lipid levels. These considerations led the panel to issue a conditional recommendation.

This recommendation is similar to that in the KDIGO guidelines, which recommends statin or statin/ezetimibe combination for adults aged ≥50 years with eGFR <60 mL/min per 1.73 m² and not undergoing kidney transplantation or chronic dialysis. In addition, the guidelines suggest considering statin treatment for patients with at least one of the following disorders: known coronary heart disease, DM, previous ischemic stroke, or estimated 10-year risk of coronary death or nonfatal myocardial infarction >10%.¹⁹ The guideline considers that the use of statins is probably feasible and acceptable.

Question 39. Should oral low-dose aspirin vs. no aspirin be used for adults with T2DM, DKD, and established ischemic CVD for secondary prevention of cardiovascular events?

Recommendation 37. *For secondary prevention of cardiovascular events in adults with T2DM and DKD, we recommend oral low-dose aspirin over no treatment (Strong recommendation, moderate evidence).*

Rationale. The recommendation is based on prospective observational cohorts and a meta-analysis that evaluated oral low-dose aspirin in patients with CKD.^{161,162}

A non-randomized cohort study (N = 3664) showed a beneficial effect of aspirin on lowering the risk of death (HR 0.89, [0.77 to 1.03]; very low certainty, [Table S38](#)), cardiovascular death (HR 0.93, [0.71 to 1.21]; very low certainty, [Table S38](#)), and composite cardiovascular outcomes (HR 1.04, [0.84 to 1.28]; very low certainty, [Table S38](#)).¹⁶¹ However, no significant difference was observed in the risk of stroke between the aspirin and no-aspirin groups (HR 1.02, [0.70 to 1.8]; very low certainty, [Table S38](#)).¹⁶¹

In a meta-analysis (n=6778) of patients with an unprovoked deep venous thrombosis or pulmonary embolus, aspirin reduced recurrent thromboembolic events (OR 0.62, [0.44 to 0.87]; moderate certainty, [Table S38](#)), and no significant difference was observed in major bleeding between aspirin treatment and the control (OR 1.28, [0.47 to 3.48]; moderate certainty, [Table S38](#)) or mortality (OR 0.95, [0.52 to 1.72]; moderate certainty, [Table S38](#)).¹⁶² While this analysis did not specifically focus on patients with DKD, it provides valuable insights owing to the lack of direct evidence.

Given the risk of recurrent cardiovascular events, including myocardial infarction, stroke, and cardiovascular death in patients with both T2DM and

DKD, the use of low-dose aspirin offers important clinical benefit. The evidence supporting a reduction in major cardiovascular events, combined with a manageable risk of bleeding, results in a favorable benefit-risk profile. The panel also considers that oral low-dose aspirin use is feasible for the secondary prevention of cardiovascular events in adults with T2DM and DKD. This supports a strong recommendation, despite the moderate certainty of evidence, which aligns with that issued in the KDIGO guidelines.¹⁹

Question 40. Should low oral doses of aspirin vs. no aspirin be used for adults with T2D and DKD for primary prevention of cardiovascular events?

Recommendation 38. *For the primary prevention of cardiovascular events in adults with T2DM and DKD, we recommend against using low oral doses of aspirin (Strong recommendation, high certainty evidence).*

Rationale. An RCT (n=2005) compared low-dose aspirin to no aspirin for primary prevention in patients with T2DM and reduced kidney function. Aspirin reduced all atherosclerotic events (HR 0.57, [0.36 to 0.88]; high certainty, [Table S39](#)) and atherosclerotic/ischemic events (HR 0.54, [0.33 to 0.86]; high certainty, [Table S39](#)) in patients with eGFR 60–89 mL/min/1.73 m². However, aspirin showed no significant benefit for atherosclerotic events (HR 1.34, [0.76 to 2.40]; moderate certainty, [Table S39](#)) or atherosclerotic/ischemic events (HR 1.29, [0.70 to 2.43]; moderate certainty, [Table S39](#)) in patients with eGFR <60 mL/min/1.73 m². Hemorrhagic events were similar between the groups, regardless of kidney function (eGFR 60–89: HR 1.03, [0.24 to 4.35]; eGFR <60: HR 0.87, [0.10 to 7.27]; moderate certainty, [Table S39](#)).¹⁶³ Gastrointestinal and cerebral bleeding incidence was infrequent and comparable in a subgroup of patients with an eGFR between 60–89 mL/min/1.73 m².

Hemorrhagic complications occurred at comparable rates between treatment groups, with the aspirin-treated cohort experiencing three gastrointestinal and four cerebral bleeding episodes compared to two gastrointestinal and four cerebral hemorrhagic events in patients not receiving aspirin therapy.¹⁶³

Recent evidence has diminished¹⁶³ aspirin's role in primary CVD prevention, indicating that its potential risks may outweigh its limited protective benefits across patient populations, which aligns with our recommendation.¹⁶⁴ According to the United States Preventive Services Task Force (USPSTF), clinicians should conduct careful individualized assessments before initiating a low-dose aspirin prescription for the primary prevention of CVD among adults aged 40–59 years and individuals with ≥10% calculated cardiovascular

disease risk over the next decade. Notably, authorities specifically advise against employing low-dose aspirin for primary cardiovascular prevention strategies in patients who have reached or exceeded 60 years of age.¹⁶⁵ The guideline panel considers the intervention as unacceptable and strongly recommends against its use owing to safety concerns.

Question 41. Should a potassium binder vs. no treatment be used in adults with hyperkalemia, T2DM, and DKD?

Recommendation 39. *For adults with T2DM, DKD, and hyperkalemia, we suggest using a potassium binder over not using it (Conditional recommendation, low certainty evidence).*

Rationale. Our evidence is based on an RCT and a meta-analysis (166,167). AMETHYST-DN was a phase 2 RCT conducted at 48 European sites (N=306). The proportion of patients with worsening CKD after 52 weeks of follow-up was significantly lower among patients with DKD and mild hyperkalemia receiving potassium binders (RR 0.38, [0.19 to 0.76]; low certainty, [Table S40](#)). The proportion of patients with hypomagnesemia and those with worsening hypertension was also lower among patients with DKD and mild hyperkalemia receiving potassium binders compared to those with moderate hyperkalemia (RR 0.52, [0.25 to 1.08] and RR 0.53, [0.25 to 1.16]; low certainty, respectively, [Table S40](#)). In addition, potassium binders reduced the proportion of patients with constipation (RR 0.26, [0.13 to 0.53], low certainty, [Table S40](#)). Regarding kidney function, no clinically meaningful differences were observed in the mean change in eGFR and albuminuria from baseline to week 52 among patients with DKD with mild or moderate hyperkalemia. The mean change in systolic and diastolic blood pressure from baseline to week 52 was similar between patients with DKD with mild or moderate hyperkalemia (15.7/8.0 mmHg and 17.1/9.2 mmHg, respectively).¹⁶⁶

A meta-analysis of 15 studies with 1849 adult participants evaluated potassium binders for chronic hyperkalemia in CKD. Twelve studies included participants with CKD (stages 1–5) who did not require dialysis, whereas three studies focused on those undergoing hemodialysis. Both RCTs and quasi-randomized studies were included. The meta-analysis demonstrated that the risk of death from any cause was lower in the potassium binders group (RR 0.69, [0.11 to 4.32]; very low certainty, [Table S40](#)); nevertheless, the risk of cardiovascular death did not significantly differ between those who received potassium binders and those who did not (RR 3.06, [0.13 to 74.24]; very low

certainty, [Table S40](#)). Furthermore, the risk of nausea and vomiting was higher among patients who received potassium binders (RR 2.10, [0.65 to 6.78], and RR 1.72, [0.35 to 8.51]; very low certainty, respectively, [Table S40](#)). Other risks, such as diarrhea, constipation, and abdominal pain, showed no significant differences. No significant impact on the risk of hypokalemia was observed (RR 1.71, [0.31 to 9.47]; very low certainty, [Table S40](#)). The health-related QoL improvement was higher in the potassium binder group (MD 2.6 points; very low certainty). Moreover, the risk of kidney transplantation was not significantly different between the groups (RR 0.34, [0.01 to 8.25]; very low certainty, [Table S40](#)).¹⁶⁷

The KDIGO guidelines suggest that potassium binders are acceptable for controlling serum potassium levels. However, they should be considered in case of diuretic or oral sodium bicarbonate treatment failure.⁴⁶ While these guidelines did not specifically target patients with DKD, they offer valuable insights. The guideline panel recognizes the low certainty of evidence, attributed to a significant risk of bias and the absence of direct evidence, resulting in a conditional recommendation for using potassium binders. They consider that the intervention would likely enhance equity and be potentially acceptable and feasible.

[Table 7](#) outlines the primary treatment strategies for DKD based on panel recommendations, whereas [Figure 1](#) presents a comprehensive algorithm for the management approach.

Discussion. In these Saudi national guidelines, we established 39 evidence-based recommendations for the comprehensive management of DKD in adult patients with T2DM, addressing key aspects of monitoring and treatment. Strong recommendations with high-to-moderate certainty evidence emphasize using SGLT-2i over metformin and sulfonylureas, highlighting their superior safety and efficacy. The guidelines strongly advocate for RAAS inhibitors (ACEIs or ARBs) over CCBs in patients with severe albuminuria while specifically recommending against ACEI/ARB combination therapy, as monotherapy would result in the same effects without resulting in adverse events. Additionally, the recommendations emphasize the importance of lifestyle modifications, including maintaining a “protein intake at 0.8g/kg body weight” and reducing sodium intake to <2 g per day.

The guidelines strongly support nonsteroidal selective MRAs for patients with normal potassium levels and appropriate eGFR. Regarding cardiovascular risk management, they strongly recommend

“low-dose aspirin for secondary prevention in patients with established CVD” but advise against its use for primary prevention. The guideline suggests a conservative medical approach over invasive strategies for patients with ischemic heart disease. Regarding glycemic management, the guideline recommends GLP-1 receptor antagonist to slow chronic kidney disease progression, reduce albuminuria, and achieve glycemic control. Moreover, it offers a conditional recommendation for adding “GLP-1 receptor agonists” to SGLT-2i in patients with unachieved targets or at increased cardiovascular risk. Moreover, the guidelines address monitoring strategies, suggesting an annual assessment of kidney function through serum creatinine and UACR measurements. These recommendations achieved remarkably high agreement among the expert panel, with most recommendations reaching 100% consensus, reflecting their robust clinical relevance and practicality.

These clinical guidelines were developed using a comprehensive, evidence-driven process complemented by experts in methodology. This methodological approach was designed to create standardized care protocols that account for the unique characteristics of Saudi healthcare systems and patient populations. The primary objective was to establish practical, implementable guidance that can be applied across variable clinical situations to enhance patient care quality and outcomes.

The recommendations were drawn from multiple levels of evidence, ensuring the highest quality of evidence and prioritizing systematic reviews and meta-analyses when available, while also incorporating data from RCTs and observational studies. Furthermore, the multidisciplinary nature of the development team, encompassing specialists from various medical fields, enriched the guidelines with diverse clinical perspectives and real-world expertise specific to the Saudi healthcare context.

Nevertheless, certain limitations warrant consideration. A significant constraint was the scarcity of high-quality research specific to the Saudi population, particularly regarding health economics and nationwide clinical outcomes. Additionally, the heterogeneous nature of the investigated populations and regional differences in healthcare resources and infrastructure present potential barriers to uniform implementation of these recommendations across all Saudi healthcare settings. Additionally, implementing these guidelines within the Saudi healthcare system presents several challenges that require strategic consideration. The variability and availability of healthcare resources

Table 7 - Strength and level of evidence for the recommendations for pharmacologic interventions for adults with DKD.

Recommendations	Strength of recommendation	Certainty of evidence	Percentage of panel agreement
8. For adults with T2DM, DKD, and severely increased albuminuria (ACR >300 mg/day), we recommend using RAAS inhibitors (ACEIs or ARBs) over CCBs. Remarks: ACEIs /ARBs should be titrated to the maximally tolerated/highest approved dose to achieve benefits. The current statement may imply administering the highest dose at treatment initiation.	Strong	Moderate	100%
9. For adults with T2DM, DKD, and severely increased albuminuria, we recommend against using any “combination of ACEI and ARB”.	Strong	Moderate	100%
10. For adults with T2DM and DKD with a “serum potassium level ≤5 mEq/L” and “an eGFR ≥25 mL/min/1.73 m ² ”, we recommend treatment with a nonsteroidal selective MRAs	Strong	Moderate	100%
11. For slowing DKD progression among adults with T2DM, DKD, and hyperuricemia, we suggest against using xanthine oxidase inhibitors.	Conditional	Moderate	100%
12. For adults with T2DM, DKD, and unachieved triglyceride targets (≤150 mg/dL) with statin maximum tolerated doses, we suggest using Icosapent Ethyl over no treatment.	Conditional	Moderate	100%
13. For adults with T2DM, DKD, and unachieved LDL-C targets with statin maximum tolerated doses, we suggest using PCSK9 inhibitors over no treatment.	Conditional	Moderate	100%
14. For patients with DKD who require lipid-lowering treatment, we suggest using either Statin or Statin/ Ezetimibe combination. “Remarks: A statin/ Ezetimibe combination is recommended if a higher statin dose is not tolerated or the target lipid level is not achieved.”	Conditional	Moderate	100%
15. For “secondary prevention of cardiovascular events” in adults with T2DM and DKD, we recommend “oral low-dose aspirin over no treatment”.	Strong	Moderate	100%
16. For the primary prevention of “cardiovascular events” in adults with T2DM and DKD, we recommend against using low oral doses of aspirin.	Strong	High	100%
17. For adults with T2DM, DKD, and hyperkalemia, we suggest using a potassium binder over not using it.	Conditional	Low	100%
ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, DKD: Diabetic kidney disease, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, MRA: Mineralocorticoid receptor antagonist, PCSK9: Proprotein convertase subtilisin/kexin type 9			

across different regions of KSA may impact guideline adherence. For example, tertiary centers in urban areas are better equipped for comprehensive DKD management than primary care facilities in rural settings. Moreover, lifestyle modifications, such as dietary changes and physical activity recommendations, may be affected by cultural factors. Pharmacoeconomic considerations are paramount when implementing these guidelines within the Saudi context. While “SGLT-2is” and “GLP-1 receptor agonists” offer significant benefits for patients with DKD, their higher costs compared to older medications may limit accessibility, particularly in settings with budget constraints. Our cost-effectiveness analysis suggests that these novel agents may reduce long-term expenditure through the prevention of kidney failure and cardiovascular complications, despite higher initial costs.

We propose establishing a systematic update mechanism that adheres to the GRADE methodology framework to overcome these limitations. This dynamic approach will ensure the guidelines remain current and clinically relevant by continuously incorporating

emerging research findings and therapeutic advancements. Regular reassessments and updates are warranted to maintain the guidelines’ utility in clinical practice, particularly as novel treatment options emerge and our understanding of disease management evolves. We recommend tiered recommendations based on resource availability, development of computerized decision-assistance systems embedded within currently operational digital medical documentation platforms, and establishment of a national registry to track guideline adherence and patient outcomes. We propose developing a national DKD research network to coordinate these efforts, with funding allocations prioritized through the Saudi Health Research System. Finally, we encourage the widespread distribution of these guidelines across KSA to achieve the highest benefit. The effective distribution of these guidelines will be achieved through a comprehensive strategy of publication in medical journals and presentation at scientific conferences and meetings. Educational initiatives and professional development programs are required to ensure healthcare providers understand and

effectively implement these recommendations in their clinical practice.

In conclusion, these Saudi national guidelines provide a practical framework supported by high-quality evidence for managing DKD in adult patients with T2DM, addressing critical areas of monitoring and treatment. While these guidelines represent a significant step forward, addressing gaps in evidence, primarily through locally relevant research and data collection, is warranted to optimize their impact.

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