# Interpretation of the BMJ Clinical Practice Guideline: SGLT-2 Inhibitors for Adults with Chronic Kidney Disease (Postprint)

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**Date:** 2026-03-23T08:59:20+00:00

## Abstract

The "Clinical Practice Guideline for SGLT-2 Inhibitors in Adults with Chronic Kidney Disease,"published in the BMJ in October 2024, stratifies the risk of complications and progression in patients with chronic kidney disease (CKD) into four levels—low, moderate, high, and very high—based on estimated glomerular filtration rate (eGFR) and proteinuria levels. The guideline quantitatively evaluates the benefits and risks of using sodium-glucose cotransporter-2 (SGLT-2) inhibitors for patients at different risk levels and proposes stratified recommendation strategies. For instance, for adult patients with low or moderate risk of CKD progression and complications, the use of SGLT-2 inhibitors may be considered (weak recommendation); whereas for adult patients at high or very high risk, the use of SGLT-2 inhibitors is recommended (strong recommendation). This provides a basis for individualized decision-making for patients and assists general practitioners in the rational and standardized use of SGLT-2 inhibitors across various clinical scenarios. Furthermore, the web-based version of the guideline' s rapid recommendations offers highly visualized tools for presenting evidence and recommendations, facilitating quick queries by general practitioners and supporting the implementation of shared clinical decision-making between doctors and patients.

## Full Text

## Preamble

# Interpretation of the "Clinical Practice Guidelines for the Use of SGLT-2 Inhibitors in Adult Patients with Chronic Kidney Disease"

Chronic kidney disease (CKD) has become a major global public health challenge. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, originally developed as glucose-lowering agents, have demonstrated significant benefits in delaying the progression of kidney disease and reducing cardiovascular events in recent years. To standardize the clinical application of these drugs, the "Clinical Practice Guidelines for the Use of SGLT-2 Inhibitors in Adult Patients with Chronic Kidney Disease" (hereafter referred to as "the Guidelines") was recently published. This article provides a detailed interpretation of the core recommendations of the Guidelines to assist clinicians in making evidence-based decisions.

## 1. Indications and Timing of Initiation

The Guidelines emphasize that SGLT-2 inhibitors are no longer limited to patients with diabetic kidney disease (DKD). Based on high-quality evidence from large-scale clinical trials such as DAPA-CKD and EMPA-KIDNEY, the indications have been expanded to include a broader range of adult CKD patients.

### 1.1 Diabetic Kidney Disease (DKD)

For adult patients with type 2 diabetes (T2DM) and CKD, the Guidelines recommend the initiation of SGLT-2 inhibitors when the estimated glomerular filtration rate (eGFR) is $\geq 20$ mL $\cdot$ min$^{-1}$ $\cdot$(1.73 m$^2$)$^{-1}$. This recommendation applies regardless of the urinary albumin-to-creatinine ratio (UACR) level, although patients with higher UACR typically derive greater absolute benefits.

### 1.2 Non-Diabetic Chronic Kidney Disease

For patients with non-diabetic CKD (such as hypertensive nephrosclerosis or stable glomerulonephritis), SGLT-2 inhibitors are recommended for those with an eGFR $\geq 20$ mL $\cdot$ min$^{-1}$ $\cdot$(1.73 m$^2$)$^{-1}$ and a UACR $\geq 200$ mg/g. The Guidelines note that for patients with a UACR $< 200$ mg/g, while the evidence for renal protection is less robust, these agents may still be considered for their cardiovascular benefits.

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## Interpretation of BMJ Clinical Practice Guideline: SGLT-2 Inhibitors for Adults with Chronic Kidney Disease

The clinical practice guideline titled "SGLT-2 Inhibitors for Adults with Chronic Kidney Disease," published in the *BMJ* in October 2024, provides a comprehensive framework for managing chronic kidney disease (CKD). The guideline stratifies the risk of complications and disease progression in CKD patients into four levels—low, moderate, high, and very high—based on the estimated glomerular filtration rate (eGFR) and albuminuria levels. By quantifying the benefits and risks associated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors across these different risk strata, the guideline proposes a tiered recommendation strategy.

For adult patients with a low or moderate risk of CKD progression and complications, the guideline suggests that SGLT-2 inhibitors may be considered (weak recommendation). In contrast, for adult patients at high or very high risk, the use of SGLT-2 inhibitors is recommended (strong recommendation). This stratified approach provides a robust foundation for individualized clinical decision-making, assisting general practitioners in the standardized and rational use of SGLT-2 inhibitors across diverse clinical scenarios.

Furthermore, the web-based version of these rapid recommendations offers highly visualized tools for presenting evidence and recommendations. These digital resources facilitate rapid queries for general practitioners and support the implementation of shared decision-making between physicians and patients.

**Keywords:** Sodium-glucose cotransporter-2 inhibitors; Chronic kidney disease; Risk stratification; Clinical practice guidelines; Shared decision-making

**CLC Number:** R 692 **Document Code:** A

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## Abstract

The clinical practice guideline on the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in adult patients with chronic kidney disease (CKD), published in the BMJ in October 2024, stratifies patients with CKD into four risk tiers—low, moderate, high, and very high—based on estimated glomerular filtration rate (eGFR) and proteinuria levels to assess their risk of complications and disease progression. The guideline provides a quantitative evaluation of the benefits and risks of SGLT-2 inhibitors across different risk tiers and proposes a tiered recommendation strategy. For instance, for adult patients with CKD who have a low or moderate risk of disease progression and complications, the use of SGLT-2 inhibitors can be considered (weak recommendation); whereas for those with a high or very high risk, the use of SGLT-2 inhibitors is recommended (strong recommendation). This approach supports individualized decision-making for patients and assists general practitioners in the rational and standardized use of SGLT-2 inhibitors across diverse clinical settings. Additionally, the guideline' s rapid-access QU F R, ZHAO L J, ZENG XX, et al. Interpretation of BMJ clinical practice guideline: SGLT-2 inhibitors for adults with chronic kidney disease[J].

Chinese General Practice, 2026. [Epub ahead of print].



Chinese General Practice web version offers highly visualized evidence and recommendation presentation tools, facilitating quick reference for general practitioners and supporting the implementation of shared decision-making between clinicians and patients.

Keywords: Sodium-glucose transporter 2 inhibitors; Chronic kidney disease; Risk stratification; Diagnostic and treatment guideline; Physician-patient shared decision-making.

The prevalence of chronic kidney disease (CKD) among adults in China is approximately 10%, representing an independent risk factor for adverse outcomes such as cardiovascular and cerebrovascular complications [**?**]. Once CKD progresses to the end-stage, patients require long-term renal replacement therapy, such as dialysis or kidney transplantation, to sustain life. This severely impacts patient quality of life and imposes a heavy medical and economic burden.

Therefore, delaying the progression of CKD and preventing complications are essential strategies for reducing the disease burden and improving prognosis [**?**]. Currently, most pharmacological treatment guidelines for CKD are tailored for nephrologists and focus primarily on "very high-risk"patient populations, such as those with end-stage renal disease or established cardiovascular complications [**?**]. As chronic disease management shifts toward primary care, the diagnosis and treatment of non-end-stage CKD patients will inevitably transition to general practitioners (GPs). The primary battlefield for CKD pharmacologi-

cal treatment will undoubtedly be managed by GPs in the community, which holds significant practical importance for improving the overall quality of renal protection at the national level.

In recent years, sodium-glucose cotransporter 2 (SGLT-2) inhibitors have become a dual focal point of research and clinical practice in the field of chronic disease due to their combined hypoglycemic, cardioprotective, and renoprotective effects. With the continuous accumulation of evidence-based data, the indicated population for these inhibitors has expanded from patients with diabetes to those with heart failure and CKD, with benefits observed regardless of diabetic status. The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines list SGLT-2 inhibitors as a first-line treatment option for most CKD patients. However, these recommendations primarily target patients with moderate-to-severe CKD accompanied by proteinuria or heart failure. They do not fully cover the vast number of non-end-stage CKD patients encountered in primary care, which limits the operability and generalizability of the guidelines in basic clinical practice. Consequently, there is an urgent need for practice guidelines that are more aligned with general practice scenarios and can address the clinical needs of CKD patients across different risk strata.

In 2024, the MAGIC Evidence Ecosystem Foundation, the BMJ, and West China Hospital of Sichuan University jointly launched a clinical practice guideline for the use of SGLT-2 inhibitors in CKD patients, titled "SGLT-2 Inhibitors for Adults with Chronic Kidney Disease: A Clinical Practice Guideline." This guideline integrates CKD prognostic risk stratification with SGLT-2 inhibitor treatment strategies and provides stratified medication recommendations based on different prognostic risk levels to guide more precise clinical decision-making. The working group included patient representatives, general practitioners, internal medicine and endocrine specialists, nephrologists, and evidence-based methodology experts, ensuring that multidisciplinary and patient perspectives were fully represented. Based on the risk stratification system developed by KDIGO, the guideline clearly defines typical risk levels for adult CKD patients and illustrates the benefits of SGLT-2 inhibitors across different risk groups over a 5-year timeframe using absolute risk differences. In translating evidence into recommendations, the guideline adopts a "patient-centered" decision-making framework. It emphasizes not only the absolute benefits and risks of critical patient outcomes and the certainty of evidence but also fully considers the values and preferences of adult patients with different risk profiles, thereby forming stratified medication recommendations for adult CKD patients at various prognostic levels.

From the perspective of Chinese general practitioners engaged in adult CKD clinical practice, this article interprets the main content, clinical application value, and key considerations of this new clinical practice guideline.

Figure 1

Figure 1: Figure 1

## 1 指南主要推荐意见

This guideline is applicable to clinical scenarios where clinicians provide individualized medication recommendations and decision support for patients with chronic kidney disease (CKD) across different risk strata. It is not applicable to the following specific populations: (1) patients currently receiving renal replacement therapy; (2) kidney transplant recipients; (3) patients with polycystic kidney disease; (4) patients with rare kidney diseases; and (5) patients with an estimated glomerular filtration rate (eGFR) $< 20$ mL $\cdot$ min$^{-1}$ $\cdot$ (1.73 m$^2$)$^{-1}$. During the development of these recommendations, the guideline panel fully considered the absolute risk-to-benefit ratio of SGLT-2 inhibitor therapy over a five-year horizon for CKD patients. Incorporating patient values and preferences, the panel proposes the following stratified recommendations (the specific risk stratification process is detailed in

): (1) For adult patients at low or moderate risk of CKD progression and complications, the use of SGLT-2 inhibitors may be considered (weak recommendation); (2) For adult patients at high or very high risk of CKD progression and complications, the use of SGLT-2 inhibitors is recommended (strong recommendation).

When seeing CKD patients in outpatient or inpatient settings, clinicians should first determine the patient's risk category based on the stratification provided in this guideline and then refer to the corresponding recommendations. A "strong recommendation" indicates that the benefits significantly outweigh the risks and that most patients would make the same choice after being fully informed; therefore, it can be adopted as a routine clinical practice, requiring only a brief explanation to the patient regarding treatment goals and precautions. In contrast, a "weak recommendation" implies that the benefits do not significantly outweigh the risks, or that there is substantial variability in values and preferences among patients. In such cases, clinicians must engage in more comprehensive communication with the patient, objectively presenting the potential benefits, risks, treatment burden, and costs of the intervention while understanding the patient' s perspectives, concerns, and treatment preferences to reach a shared decision on whether to implement the protocol.

## 2.1 SGLT-2

## Benefits and Risks of SGLT-2 Inhibitors

The evidence regarding the benefits and risks of SGLT-2 inhibitors, as demonstrated by a meta-analysis published concurrently with this guideline, indicates that these agents significantly reduce the risk of multiple clinical outcomes in

Figure 1

Figure 2: Figure 1

patients at very high risk of CKD progression and complications. Based on a five-year treatment period, for every 1,000 patients treated,

*Chinese General Practice*. Note: SGLT-2 = sodium-glucose cotransporter 2. Among 1,000 patients with CKD, the use of SGLT-2 inhibitors can prevent 48 cases of all-cause mortality, 10 cases of cardiovascular death, 25 hospitalizations for heart failure, 58 cases of kidney failure, 32 non-fatal myocardial infarctions, and 25 non-fatal strokes. These clinical benefits are most clearly established in this population. For high-risk patients, most outcome indicators also show significant improvement, although the reductions in heart failure hospitalizations and kidney failure are relatively limited or less clearly defined.

In patients with low or moderate risk of CKD progression and complications, SGLT-2 inhibitors may offer some benefits in reducing the risk of all-cause mortality and non-fatal stroke; however, improvements in other health outcomes are relatively limited. Regarding safety evidence, although some adverse reactions may occur during the use of SGLT-2 inhibitors, the increased risks of these adverse events—including acute kidney injury requiring dialysis, fractures, amputations, ketoacidosis, genital infections, and symptomatic hypovolemia—are minimal. These risks do not reach a level that would practically impact clinical decision-making; therefore, the overall safety profile remains within an acceptable range.

## Development of Risk Stratification and Baseline Risk Estimation

This guideline adopts the eGFR and albuminuria stratification system recommended by KDIGO, classifying CKD patients into four categories based on their risk of disease progression and complications: low risk, moderate risk, high risk, and very high risk

. To further validate the prognostic differences among these risk strata, the guideline evaluated the future risks of mortality, cardiovascular events, heart failure hospitalization, and kidney failure for these four categories of CKD patients using a large-scale community population database from the United Kingdom. This allowed for the determination of baseline risk levels corresponding to each risk tier. Because the relative risk reduction of these adverse outcomes provided by SGLT-2 inhibitors is consistent across different CKD risk strata, patients with a higher baseline risk of adverse outcomes derive a greater absolute clinical benefit. For example, after using SGLT-2 inhibitors, the absolute risk reduction for all-cause mortality is 7 cases per 1,000 people in low-risk CKD patients, 13 cases in moderate-risk patients, 24 cases in high-risk patients, and 48 cases in very-high-risk patients.

Figure 1

Figure 3: Figure 1

### 2.3 临床实践中的患者价值观与偏好

As a chronic disease, every critical decision in the management of Chronic Kidney Disease (CKD) should be integrated with the patient' s specific clinical context. Clinicians must not only focus on the disease itself but also place significant importance on the patients' perspectives regarding their own health (i.e., their values), as well as their preferences for choices made during the health promotion process and the underlying reasons for these preferences [**?**]. However, these patient-centered decision-making elements are frequently overlooked in clinical practice. In addition to evaluating the risk-benefit balance of key clinical outcome indicators and the reliability of the evidence, this BMJ Rapid Recommendation guideline identifies the values and preferences of CKD patients as a primary focus for its recommendations.

In practice, every clinical consultation requires a systematic assessment of the patient' s values and preferences. A representative question often asked is: "What concerns you most about your kidney disease?" Most patients tend to worry about so-called "kidney damage" and the potential future need for renal replacement therapy, such as dialysis. The former concern is closely related to traditional Chinese medicine (TCM) perceptions in our country, while the latter often stems from cultural media portrayals and the lived experiences of relatives and friends. Even with identical clinical presentations, the significance of symptoms can vary significantly between different patients. For example, edema—

Flowchart of risk stratification system

Edema is a common symptom during the progression of Chronic Kidney Disease (CKD). However, patients' perceptions of this condition vary significantly: some pay little attention to mild edema, while others find it distressing when it interferes with their choice of footwear or clothing. Furthermore, some patients may experience heightened levels of concern and anxiety regarding edema, often influenced by the past experiences of family members.

During the clinical diagnosis and treatment process, clinicians should prioritize identifying a patient' s true values versus anxiety reinforced by external factors. Some patients focus intensely on serum creatinine and urinary protein levels. However, these laboratory indicators are not directly perceptible to the patient; their primary role is as auxiliary tools to help doctors and patients collectively assess disease prognosis. Focusing solely on fluctuations in individual values often leads to neglecting the more critical overall clinical status. Furthermore, random errors caused by testing methods or specimen collection techniques can trigger unnecessary panic. A patient' s concern regarding laboratory indicators is often linked to previous clinical encounters where physicians overemphasized

these metrics. Therefore, in the diagnosis, treatment, and long-term management of Chronic Kidney Disease (CKD), clinical focus should return to the patient' s actual health status rather than relying on "surrogate endpoints" such as laboratory values.

Based on discussions among global multidisciplinary experts and patient peers, this guideline posits that mortality, cardiovascular events, end-stage renal disease (initiation of dialysis), quality of life, and adverse drug reactions (such as reproductive tract infections) are the clinical endpoints of greatest concern and value to CKD patients. Investigations into patient values and preferences regarding SGLT-2 inhibitors in the CKD population indicate that when evidence demonstrates certain and clinically significant benefits with low medication risk, the majority of CKD patients are willing to use these drugs. Conversely, if the therapeutic benefits are limited or uncertain, most patients tend to decline the medication even if the risks are minimal.

Consequently, based on the evidence for SGLT-2 inhibitors and patient values and preferences, the guideline provides differentiated recommendations for patients at different risk levels:

- **For patients at high and very high risk of CKD progression and complications:** Because SGLT-2 inhibitors offer clear and substantial benefits in reducing mortality, kidney failure, and cardiovascular disease without significantly increasing adverse events, the guideline panel inferred that all or nearly all patients would choose this treatment after being informed. Therefore, a **strong recommendation** was issued.
- **For low-to-moderate risk patients:** Because the overall benefits are limited and individual values vary significantly, it is anticipated that most —but not all—patients would be willing to accept the treatment. Therefore, a **weak recommendation** was issued.

## 3 指南优势及与其他指南的比较

The 2022 KDIGO *Clinical Practice Guideline for Diabetes Management in CKD* marked a paradigm shift by reclassifying SGLT-2 inhibitors from glucose-lowering agents to core renoprotective therapies for patients with diabetes and CKD. This guideline emphasized their dual cardio-renal benefits, and by 2024, the recommended population was expanded to include CKD patients both with and without diabetes, signaling a significant elevation of the drug' s status in nephrology management. It is important to note, however, that the KDIGO recommendations are primarily based on meta-analyses of four major randomized controlled trials, and their scope is limited to specific high-risk groups (i.e., those with an eGFR $\geq 20$ mL $\cdot$ min$^{-1}$ $\cdot$ (1.73 m$^2$)$^{-1}$).

Specifically, this includes patients with a urinary albumin-to-creatinine ratio (ACR) $>$ 20 mg/mmol who also suffer from heart failure, or those with an eGFR between 20 and 45 mL $\cdot$ min$^{-1}$ $\cdot$ (1.73 m$^2$)$^{-1}$.

Additionally, it covers patients with an eGFR $\geq$ 20 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ who have an ACR $<$ 20 mg/mmol.

More importantly, the KDIGO guidelines do not provide detailed explanations of the stratified effects across different baseline risks. Consequently, they offer limited support for more refined, risk-oriented medication strategies.

In contrast, this version of the BMJ guideline is based on a comprehensive literature review of SGLT-2 inhibitors used in CKD patients. By utilizing the existing KDIGO risk stratification framework, it provides differentiated recommendations for patients at various risk levels, thereby avoiding a "one-size-fits-all" approach to treatment. Furthermore, the guideline employs visualization tools to provide quantitative data on risks and benefits, facilitating shared decision-making between physicians and patients.

## 4 临床的实操策略及注意事项

When utilizing SGLT-2 inhibitors in the Chronic Kidney Disease (CKD) population, clinical management should be refined by integrating individual patient characteristics into the overall risk-benefit assessment. For populations with specific high-risk factors, the standard benefit-risk conclusions applicable to general CKD patients may not be entirely appropriate. Consequently, clinicians should develop more cautious and dynamic medication strategies within the framework of evidence-based medicine and guideline recommendations, while carefully considering comorbidities, concomitant drug use, and medical history.

For patients at high risk of urogenital infections, SGLT-2 inhibitors may increase the risk of genital tract infections. Therefore, a comprehensive assessment of infection risk must be completed prior to initiating treatment with these agents in the chronic kidney disease (CKD) population.

For general patients with chronic kidney disease (CKD), SGLT-2 inhibitors can be administered under routine follow-up and monitoring. However, for populations at high risk of urogenital infections—such as those with a history of recurrent urogenital infections, structural abnormalities of the urinary system, severe underlying diseases, or compromised immune function—or for patients who have previously experienced infection-related adverse reactions due to SGLT-2 inhibitors, the individualized risk-benefit balance must be weighed more cautiously. In such cases, initiating or re-initiating the medication may be avoided if necessary.

For patients already receiving SGLT-2 inhibitors, health education and proactive monitoring should be strengthened. Patients should be instructed to maintain urogenital hygiene and ensure adequate water intake; specifically, female patients are advised to perform perineal cleaning at least once daily. Furthermore, it is essential to improve all patients' ability to recognize early symptoms of infection. Common symptoms suggestive of urogenital infections include urinary frequency, urgency, dysuria, a burning sensation during urination, abnormal

discharge, and itching or discomfort of the vulva or glans. If these symptoms occur, patients should seek medical evaluation promptly and receive standardized anti-infective treatment. If more severe symptoms develop, such as intense perineal pain, tenderness, or fever, clinicians should be highly alert to the possibility of necrotizing fasciitis (Fournier' s gangrene), which requires immediate discontinuation of the SGLT-2 inhibitor and urgent surgical intervention.

## Populations at High Risk for Diabetic Ketoacidosis

SGLT-2 inhibitors can increase the risk of developing diabetic ketoacidosis (DKA) [**?**, **?**]. Although the overall risk of SGLT-2 inhibitor-induced DKA in the general population is extremely low, this risk can rise significantly under specific clinical circumstances. Therefore, an individualized assessment must be conducted prior to prescribing the medication. High-risk populations for DKA include those with a previous history of the condition.

Patients who have previously experienced diabetic ketoacidosis (DKA), those undergoing prolonged fasting, individuals on very-low-carbohydrate diets, or those with inadequate nutritional intake due to illness are at increased risk [18-19]. Other high-risk groups include individuals with excessive alcohol consumption, severe diarrhea, dehydration, or acute severe infections, as well as patients who have undergone gastrointestinal surgery. Furthermore, patients with type 1 diabetes or those with type 2 diabetes who may have insufficient insulin secretion are also susceptible. For these populations, the risk-benefit ratio must be thoroughly evaluated before initiating SGLT-2 inhibitors. If necessary, clinicians should consider avoiding these medications or delaying their initiation —or resumption—until the high-risk conditions predisposing the patient to DKA have been fully corrected.

It is noteworthy that sodium-glucose cotransporter-2 (SGLT-2) inhibitor-associated diabetic ketoacidosis (DKA) often presents as "euglycemic or mildly hyperglycemic DKA." In these cases, blood glucose levels at onset typically do not exceed 13.9 mmol/L, making the condition more susceptible to being overlooked in clinical practice [**?**].

To reduce the risk of missed diagnoses, patient education should be strengthened to ensure a thorough understanding of the clinical manifestations and common triggers of ketoacidosis. If symptoms such as fatigue, extreme thirst, unexplained vomiting, abdominal pain, dehydration, or confusion occur during medication use, patients should immediately suspend the use of SGLT-2 inhibitors and test for blood or urinary ketones as soon as possible. Once DKA is confirmed, standardized treatment should be administered promptly following the discontinuation of the drug.

## Populations Using Combined Renoprotective Medications

The progression of cardio-renal disease in patients with diabetic kidney disease (DKD) is driven by multiple coexisting pathological mechanisms. These include glomerular hyperfiltration, activation of the renin-angiotensin system (RAS), and abnormalities in inflammatory and fibrotic pathways. Because a single pharmacological agent is rarely able to address all of these critical pathways simultaneously, patients with severe disease or those in a state of rapid progression often require the combined use of multiple drugs that have demonstrated benefits for renal endpoints.

Against this backdrop, Chinese scholars have for the first time proposed the "Renal Triple Therapy" (RTT) strategy specifically for populations with type 2 diabetes and chronic kidney disease (CKD). This strategy comprises three pillars of DKD treatment: renin-angiotensin system inhibitors (RASi), the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

It is essential to emphasize that all three classes of medications may cause a transient increase in serum creatinine and a corresponding decrease in the estimated glomerular filtration rate (eGFR) during the initial phase of treatment. The common physiological basis for this phenomenon is that these agents regulate glomerular hemodynamics through different mechanisms, thereby reducing the state of glomerular hyperfiltration and lowering intraglomerular pressure.

When formulating a treatment plan for RTT, general practitioners should inform patients in advance that all three medications may affect renal function indicators during the early stages of treatment. It is essential to emphasize that these changes are typically predictable; providing this information prevents patients from misinterpreting the data as "deteriorating kidney function" and prematurely discontinuing their medication due to a lack of pharmacological understanding. Furthermore, a sequential initiation strategy is recommended over the simultaneous introduction of all drugs. This approach allows clinicians to observe the patient' s tolerance to each specific medication individually while facilitating the dynamic monitoring of electrolyte levels and renal function.

During RTT treatment, the monitoring and management of renal function changes induced by SGLT-2 inhibitors and related medications should follow the recommendations of the KDIGO guidelines. According to these guidelines, if the estimated glomerular filtration rate (eGFR) decreases by $\leq 30\%$ following the initiation of SGLT-2 inhibitor therapy, treatment discontinuation is not required. However, if the eGFR decline exceeds 30%, clinicians must first investigate and identify potential confounding factors for renal impairment, such as hypovolemia, infection, heart failure, or the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).

If the estimated glomerular filtration rate (eGFR) continues to decline after correcting potential triggers, a dose reduction or discontinuation of the medication

should be considered. The early eGFR fluctuations associated with finerenone and Renin-Angiotensin System inhibitors (RASi) are similar to those observed with Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors; therefore, monitoring strategies for the latter can serve as a reference. Generally, the eGFR decline caused by SGLT-2 inhibitors tends to stabilize after approximately two months, whereas eGFR levels typically return to baseline within one month after the discontinuation of finerenone.

For patients with a low baseline eGFR (such as those in CKD stage 3b or later), the reduction in renal functional reserve makes them more sensitive to hemodynamic changes. Consequently, these patients are more prone to fluctuations in serum creatinine and eGFR following the initiation of Renin-Angiotensin-Aldosterone System Triple Therapy (RTT). Such patients are also at a higher risk of premature drug discontinuation due to eGFR decline, or may even reach thresholds where the medication becomes contraindicated. In these clinical scenarios, a comprehensive judgment—integrating the identification of underlying triggers, individualized risk assessment, and dynamic monitoring results—is essential to determine whether to temporarily suspend or adjust the treatment regimen.

Furthermore, hyperkalemia is the primary reason for the discontinuation of Renin-Angiotensin System inhibitors (RASi) and finerenone [**?**, **?**]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that when hyperkalemia occurs, priority should be given to potassium-lowering measures (such as diuretics or oral potassium binders) rather than immediate dose reduction or discontinuation of the primary therapy. Meta-analysis results suggest that while the combined use of RASi and Mineralocorticoid Receptor Antagonists (MRA) significantly increases the risk of hyperkalemia, the addition of Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors can significantly mitigate this risk. This suggests that the RTT (RASi, SGLT-2i, and MRA) triple therapy may possess a distinct advantage in stabilizing serum potassium levels, although further high-quality evidence-based results are required for definitive validation.

For patients with a lower baseline estimated glomerular filtration rate (eGFR), the risk of hyperkalemia is further elevated. It is recommended to increase the frequency of blood potassium monitoring and to adjust treatment strategies in a timely manner based on changes in the patient' s renal function.

It should be noted that combining glucagon-like peptide-1 receptor agonists (GLP-1RA) with RTT (Renin-Angiotensin System Inhibition Therapy) can improve glycemic control and weight management while further reducing proteinuria and exerting regulatory effects on renal inflammation. This combination is particularly suitable for patients with Chronic Kidney Disease (CKD) who have poorly controlled blood glucose or comorbid obesity. The 2024 KDIGO guidelines explicitly state that for patients with Type 2 Diabetes Mellitus (T2DM) and CKD, long-acting GLP-1RAs should be administered if treatment goals are not met with metformin and SGLT-2 inhibitors, or if these medications are not

tolerated.

Whether utilizing the "Triple Therapy" or the potential future "Quadruple Therapy" models for renal protection, clinicians must account for the diminished metabolic capacity in CKD patients, which increases the risk of drug accumulation and toxicity. Consequently, drug selection and dosage must be based on a comprehensive assessment of multiple factors, including the stage of renal function, cardiovascular risk, comorbidities, and drug tolerance. Physicians should develop individualized strategies characterized by a gradual titration of medications and dynamic monitoring of renal function, electrolytes, and clinical tolerance. Such an approach is essential to maximize therapeutic benefits while minimizing adverse reactions, particularly when the estimated glomerular filtration rate (eGFR) is between 20-30 mL/min/1.73m$^2$.

It should be noted that this guide is applicable to patients with an estimated glomerular filtration rate (eGFR) $\geq 20$ mL $\cdot$ min$^{-1}$ $\cdot$(1.73 m$^2$)$^{-1}$.

For patients with Chronic Kidney Disease (CKD), this threshold is primarily based on evidence provided by large-scale randomized controlled trials (RCTs) conducted in recent years. Previously, some pharmaceutical instructions and early studies typically utilized an estimated glomerular filtration rate (eGFR) of $> 25$ or 30 mL $\cdot$ min$^{-1}$ as the threshold for initiating treatment. However, as clinical evidence has accumulated, the lower limit of renal function for inclusion in clinical trials has gradually decreased. For example, the EMPA-KIDNEY trial further lowered the inclusion criteria to 20 mL $\cdot$ min$^{-1}$ [**?**].

Furthermore, it has been confirmed that SGLT-2 inhibitors continue to provide clear renal and cardiovascular benefits within this range. This threshold is also consistent with both international and domestic guidelines.

For example, the KDIGO 2024 CKD Guideline and the *Chinese Expert Consensus on the Clinical Application of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Chronic Kidney Disease (2023 Edition).*

[28] all suggest that it is appropriate to use when the estimated glomerular filtration rate (eGFR) is $\geq 20$ mL $\cdot$ min$^{-1}$.

The initiation of SGLT-2 inhibitor therapy in patients with Chronic Kidney Disease (CKD) requires careful consideration. Currently, evidence from randomized controlled trials remains relatively limited for certain subgroups. Furthermore, patients at advanced stages often present with severe renal insufficiency, unstable volume status, or are nearing the stage of renal replacement therapy, making clinical decision-making complex and dependent on multiple clinical factors. Consequently, this guideline does not include these specific populations within its scope of recommendation.

For patients with an eGFR between 20–30 mL $\cdot$ min$^{-1}$ $\cdot$ (1.73m$^2$)$^{-1}$ and those with an eGFR $<$20 mL $\cdot$ min$^{-1}$ $\cdot$ (1.73m$^2$)$^{-1}$, the clinical application of SGLT-2 inhibitors necessitates more rigorous monitoring compared to populations with

better preserved renal function. Particular emphasis should be placed on monitoring renal function, assessing volume status, and evaluating concomitant medications. This is especially critical when SGLT-2 inhibitors are used in combination with diuretics or Renin-Angiotensin-Aldosterone System (RAAS) inhibitors. In such cases, blood pressure and renal function must be closely monitored to enhance both the safety and accessibility of the treatment.

### Other Special Populations

Previous research reports suggest that SGLT-2 inhibitors may increase the risk of falls and fractures by inducing hypovolemia [**?**]. Therefore, a systematic assessment of the patient' s blood volume status is essential before initiating SGLT-2 inhibitor therapy. This assessment should include a review of the patient' s medical history regarding baseline blood pressure levels, recent blood pressure fluctuations, and any history of orthostatic hypotension or syncope. Clinicians should also inquire about recent symptoms such as vomiting or diarrhea. During the physical examination, specific attention should be paid to heart rate, blood pressure, and skin turgor to ensure a comprehensive evaluation of the patient' s fluid status.

Blood pressure and volume status should be dynamically monitored during medication use [**?**]. If symptoms of hypotension occur, such as dizziness or fatigue, the dosage of antihypertensive drugs or diuretics should be adjusted first; if necessary, SGLT-2 inhibitors should be suspended or discontinued. For patients concurrently using loop diuretics, elderly populations, or those with poor baseline renal function, the risk of hypovolemia-related adverse events is further increased, necessitating enhanced follow-up and monitoring.

Some evidence synthesis studies suggest that SGLT-2 inhibitors may be associated with risks of prostate cancer and amputation [**?**, **?**, **?**, **?**]. For patients with comorbid urogenital tumors, these drugs should be used with relative caution, and tumor-related follow-up should be strengthened. In patients with comorbid lower extremity arterial stenosis, an individualized risk-benefit assessment is particularly required. Caution should be exercised when using this class of drugs, represented by canagliflozin, in such populations [**?**, **?**]. When use is deemed necessary, lower limb blood supply, sensory function, and foot skin integrity should be systematically evaluated prior to administration, and regular foot examinations should be performed during the course of treatment.

## Stratified Implementation Strategies Across Diverse Medical Resource Contexts

In real-world clinical practice, the accessibility and affordability of medications are critical factors determining whether clinical guidelines can be successfully implemented. Currently, SGLT-2 inhibitors such as dapagliflozin and empagliflozin have been included in the National Reimbursement Drug List (NRDL). As the scope of approved indications expands, the proportion of out-

of-pocket costs for patients has further decreased, thereby enhancing the overall accessibility of these drugs. However, significant disparities remain in the actual payment capacity and willingness of different patient populations. These variations are driven by factors such as regional economic development levels, the distribution of medical resources, and differences in the execution of local health insurance policies.

Against this background, the risk-stratification-based recommendation strategy proposed in this guideline demonstrates significant flexibility and practical feasibility at the clinical implementation level. In regions where medical resources are relatively limited, treatment priorities can be focused on high-risk and very-high-risk patients with Chronic Kidney Disease (CKD). This approach ensures the maximization of clinical benefits and resource utilization efficiency under constrained conditions. Conversely, in regions with more abundant medical resources, the scope of treatment can be expanded to include low-to-moderate risk patients, provided that safety is maintained and patient values and preferences are respected. Such an expansion facilitates broader prevention of renal and cardiovascular diseases.

## 5 总结

As a BMJ Rapid Recommendation based on the latest evidence, the "Clinical Practice Guideline for SGLT-2 Inhibitors in Adults with Chronic Kidney Disease (CKD)" provides a refined and individualized decision-making framework for the clinical application of SGLT-2 inhibitors, centered on patient risk stratification. The guideline states that for patients with high-risk and very high-risk CKD, SGLT-2 inhibitors offer clear and clinically significant benefits; therefore, their routine use is recommended. Conversely, for CKD patients with low-to-moderate risk of complications, SGLT-2 inhibitors are not routinely recommended. In these cases, clinicians should develop personalized treatment strategies by integrating the patient' s specific clinical circumstances with their values and preferences.

This stratification strategy is particularly applicable to general practitioners treating CKD patients in outpatient or primary care settings. It facilitates more rational treatment prioritization under conditions of limited medical resources and promotes the standardized and precise use of SGLT-2 inhibitors at the primary care level. Furthermore, the guideline has been launched on the MAGICapp platform, providing visualized evidence summaries and interactive clinical decision support tools. These resources enable clinicians to quickly access quantified risk-benefit information, enhancing decision-making transparency and further promoting the implementation of the guideline across different levels of healthcare.

**Author Contributions:** Furong Qu was responsible for drafting and writing the manuscript; Lijun Zhao, Xiaoqian Zeng, and Jing Li provided suggestions; Sheyu Li proposed the research concept; Sheyu Li and Jing Li revised the

manuscript, finalized the version, and take overall responsibility for the article.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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## Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

### Introduction

Chronic Kidney Disease (CKD) remains a significant global health challenge, necessitating standardized approaches for diagnosis, risk stratification, and therapeutic intervention. This guideline, published in *Kidney International* (2024), provides an updated framework for clinicians to manage CKD effectively, incorporating recent advancements in nephrology and evidence-based medicine.

### Evaluation of Chronic Kidney Disease

The evaluation of CKD centers on the assessment of glomerular filtration rate (GFR) and albuminuria. The guideline emphasizes the use of standardized equations for estimating GFR (eGFR) from serum creatinine and, where appropriate, cystatin C. Accurate classification of CKD stages is essential for determining prognosis and guiding treatment intensity.

Beyond initial diagnosis, the guideline recommends comprehensive screening for underlying etiologies, including diabetes mellitus, hypertension, and primary glomerulonephritides. Longitudinal monitoring of eGFR and the urine albumin-to-creatinine ratio (UACR) is critical to track disease progression and evaluate the efficacy of interventions.

### Management Strategies

The primary goals of CKD management are to delay the progression to kidney failure and reduce the risk of cardiovascular complications. Key therapeutic

Figure 1

Figure 4: Figure 1

pillars include:

1. **Blood Pressure Control:** Targeted blood pressure management is vital. The guideline supports individualized targets, generally recommending a systolic blood pressure of $< 120$ mmHg when measured standardizedly, provided it is well-tolerated.
2. **Pharmacological Interventions:** The use of Renin-Angiotensin System (RAS) inhibitors, such as ACE inhibitors or ARBs, remains the gold standard for patients with hypertension and albuminuria. Furthermore, the guideline highlights the transformative role of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors in reducing the risk of CKD progression and cardiovascular events across a broad range of patients.
3. **Glycemic Control:** For patients with concomitant diabetes, achieving optimal glycemic targets is essential to prevent microvascular damage.
4. **Lifestyle Modifications:** Dietary adjustments, including moderate protein intake and sodium restriction, along with regular physical activity and smoking cessation, are strongly encouraged.

### Risk Stratification and Referral

Effective management requires a risk-based approach. The guideline utilizes the "heat map" framework, which combines GFR categories and albuminuria stages to predict the risk of progression, acute kidney injury, and cardiovascular mortality.

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## Abstract

**Background:** Cardiovascular disease (CVD) remains a leading cause of global mortality. While pharmacological interventions for primary and secondary prevention are effective, patient adherence is heavily influenced by individual values and preferences regarding medication habits. Understanding these preferences is crucial for shared decision-making and improving clinical outcomes.

**Objective:** To explore the values and preferences of patients regarding medication habits in the context of primary and secondary prevention of CVD using an exploratory mixed-methods approach.

**Methods:** This study employed a sequential exploratory mixed-methods design. In the qualitative phase, semi-structured interviews were conducted with patients at risk of or diagnosed with CVD to identify key themes influencing medication preferences. These findings informed the development of a quantitative survey administered to a larger cohort to validate and quantify these preferences. Data integration was achieved through a triangulation protocol.

**Results:** Qualitative analysis revealed four primary themes: perceived necessity of medication, concerns regarding side effects, the burden of medication

regimens, and the influence of healthcare provider communication. Quantitative results indicated that patients in the secondary prevention group prioritized efficacy and long-term safety, while those in the primary prevention group were more sensitive to medication costs and the complexity of daily dosing schedules. Statistical analysis showed significant differences in preference weights between the two groups ($P < 0.05$).

**Conclusion:** Patients' values and preferences for CVD medication are multifaceted and differ significantly between primary and secondary prevention contexts. Clinicians should adopt personalized treatment strategies that align with patient preferences to enhance medication adherence and optimize cardiovascular health management.

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## Introduction

Cardiovascular disease (CVD) continues to be a major public health challenge, accounting for a significant proportion of the global disease burden. Effective management strategies, including both primary prevention for high-risk individuals and secondary prevention for those with established disease, rely heavily on long-term medication adherence. However, clinical practice often reveals a gap between evidence-based prescriptions and actual patient behavior.

Recent shifts toward patient-centered care emphasize the importance of incorporating patient

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## Abstract

Obesity has become a global public health challenge, significantly increasing the risk of metabolic diseases such as type 2 diabetes and cardiovascular disease. Dietary intervention remains the cornerstone of obesity management. Among various nutritional strategies, low-carbohydrate diets (LCD) and low-fat diets (LFD) are the most widely discussed and debated. This review synthesizes current clinical evidence regarding the efficacy and safety of LCD and LFD in weight loss, glycemic control, and lipid metabolism. While both interventions can achieve significant weight reduction in the short term, their long-term sustainability and metabolic impacts differ. LCDs often show superior results in rapid weight loss and improving insulin sensitivity, whereas LFDs are tradition-

ally associated with cardiovascular health. This article aims to provide clinicians with a comprehensive understanding of these dietary patterns to facilitate personalized nutritional therapy for obese adults.

## Introduction

The prevalence of obesity is rising rapidly worldwide, leading to a substantial burden on healthcare systems. Effective weight management is essential for preventing and treating obesity-related comorbidities. Dietary intervention is recognized as the primary and most cost-effective approach to weight loss. Historically, low-fat diets (LFD) were recommended as the standard for weight reduction based on the high energy density of fats. However, in recent decades, low-carbohydrate diets (LCD) have gained significant popularity due to their potential metabolic advantages.

Despite extensive research, the debate over which dietary pattern is superior remains unresolved. The effectiveness of these diets often depends on individual adherence, metabolic phenotype, and the quality of macronutrients consumed. This review evaluates the physiological mechanisms, clinical outcomes, and potential risks associated with LCD and LFD in the context of adult obesity management.

## 1. Low-Carbohydrate Diets (LCD)

### 1.1 Definition and Classification

Low-carbohydrate diets typically restrict carbohydrate intake to less than 26% of total daily energy or less than 130 g/day. Very-low-carbohydrate diets (VLCD), often referred to as ketogenic diets (KD), further restrict carbohydrates to less than 10% of total energy or 20–50 g/day to induce

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## "Renal Triple Therapy" : Treatment Strategies for Type 2 Diabetes Combined with Chronic Kidney Disease

**Sun Lin, Li Li.** "Renal Triple Therapy" : Treatment Strategies for Type 2 Diabetes Combined with Chronic Kidney Disease [J]. *National Medical Journal*

*of China*, 2025, 105(12): 867-871. DOI: 10.3760/cma.

## Abstract

The prevalence of type 2 diabetes mellitus (T2DM) combined with chronic kidney disease (CKD) is high, and it carries a significant risk of progressing to end-stage renal disease (ESRD) and cardiovascular events. In recent years, major breakthroughs in clinical trials have established a new foundational treatment framework. This "Renal Triple Therapy" —consisting of Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i), Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA), and non-steroidal Mineralocorticoid Receptor Antagonists (ns-MRA)—has demonstrated synergistic effects in providing cardiorenal protection. This article explores the mechanisms, clinical evidence, and implementation strategies of this triple therapy to provide a reference for the standardized management of patients with T2DM and CKD.

## Introduction

Chronic kidney disease (CKD) is one of the most serious complications of type 2 diabetes mellitus (T2DM). Diabetic kidney disease (DKD) has become the leading cause of end-stage renal disease (ESRD) worldwide. Despite the long-standing use of Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (ARB) as the standard of care to inhibit the Renin-Angiotensin-System (RAS), the residual risk of renal progression and cardiovascular mortality remains high.

Recent pharmacological advancements have shifted the treatment paradigm from simple glycemic and blood pressure control to comprehensive organ protection. The emergence of SGLT2i, GLP-1RA, and ns-MRA has revolutionized the management of T2DM and CKD. The combined application of these three classes of drugs, often referred to as the "Renal Triple Therapy," targets multiple pathophysiological pathways including metabolic dysfunction, hemodynamic instability, inflammation, and fibrosis.

## 1. The Components of "Renal Triple Therapy"

### 1.1 SGLT2 Inhibitors (SGLT2i)

SGLT

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## Chinese Expert Consensus on the Management of Hypertension in Adults with Type 2 Diabetes

**Diabetes and Obesity Study Group of the Chinese Diabetes Society, Chinese Hypertension League, Zhu Zhiming, et al.**

### 1 Introduction

The prevalence of type 2 diabetes mellitus (T2DM) and hypertension is increasing annually in China, and the two conditions frequently coexist. Hypertension is a major risk factor for macrovascular and microvascular complications in patients with T2DM, significantly increasing the risk of cardiovascular events, stroke, and chronic kidney disease. Effective management of blood pressure (BP) is essential for improving the long-term prognosis of these patients.

In recent years, several large-scale clinical trials and observational studies have provided new evidence regarding BP targets, pharmacological interventions, and lifestyle modifications for patients with comorbid T2DM and hypertension. To standardize clinical practice and improve the quality of care, the Diabetes and Obesity Study Group of the Chinese Diabetes Society, in collaboration with the

Chinese Hypertension League, has developed this expert consensus based on the latest domestic and international guidelines and clinical evidence.

## 2 Epidemiology and Pathophysiology

The coexistence of hypertension and T2DM is common, with studies indicating that approximately 60% to 80% of patients with T2DM also suffer from hypertension. The pathophysiological mechanisms linking these two conditions are complex and bidirectional. Insulin resistance and hyperinsulinemia can lead to increased sympathetic nervous system activity and renal sodium reabsorption, contributing to elevated BP. Conversely, hypertension-induced vascular damage and oxidative stress can exacerbate insulin resistance.

Common underlying factors include obesity, chronic inflammation, and activation of the renin-angiotensin-aldosterone system (RAAS). Addressing these shared pathways is critical for the integrated management of both metabolic and hemodynamic abnormalities.

## 3 Diagnosis and Evaluation

**3.1 Blood Pressure Measurement** Accurate BP measurement is the foundation of management. In addition to office blood pressure (OBP), the use of home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) is strongly encouraged to identify "white coat hypertension" and "masked hypertension."

**3.2 Clinical Evaluation** Patients with T2DM and hypertension should undergo a comprehensive evaluation, including: - Assessment of cardiovascular risk factors (e.g., dyslipidemia, smoking, obesity). - Screening for target organ damage (e.g., left ventricular hypertrophy, carotid intima-media thickness). - Evaluation of diabetic complications (e.g., diabetic

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