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RAPID RECOMMENDATIONS

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors for adults with chronic kidney disease: a clinical practice guideline

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ABSTRACT

CLINICAL QUESTION

What is the impact of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on survival and on cardiovascular and kidneyoutcomes for adults living with chronic kidney disease (CKD)?

CURRENT PRACTICE

Few therapies slow kidney disease progression and improve long term prognosis for adults living with CKD. SGLT-2 inhibitors have demonstrated cardiovascular and kidney benefits in adults with CKD with and without type 2 diabetes. Existing guidance for SGLT-2 inhibitors does not account for the totality of current best evidence for adults with CKD and does not provide fully stratified treatment effects and recommendations across all risk groups based on risk of CKD progression and complications.

RECOMMENDATIONS

The guideline panel considered evidence regarding benefits and harms of SGLT-2 inhibitor therapy for adults with CKD over a five year period, along with contextual factors, and provided the following recommendations:

1. For adults at low risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)
2. For adults at moderate risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)
3. For adults at high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)
4. For adults at very high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour).

Recommendations are applicable to all adults with CKD, irrespective of type 2 diabetes status.

HOW THIS GUIDELINE WAS CREATED

An international panel including patients, clinicians, and methodologists produced these recommendations following standards for trustworthy guidelines and using the GRADE approach. The panel identified typical risk strata of adults with CKD (from low to very high risk of CKD progression and related complications) using the classification system developed by Kidney Disease Improving Global Outcomes (KDIGO), and applied an individual patient perspective in moving from evidence to recommendations. Effects of SGLT-2 inhibitors were interpreted in absolute terms applicable to different risk strata with varying baseline risks for outcomes of benefit over a five year period. The panel explicitly considered the balance of benefits, harms, and burdens of starting an SGLT-2 inhibitor, incorporating the values and preferences of adults with different risk profiles. Interactive evidence summaries and decision aids accompany multilayered recommendations, developed in an online authoring and publication platform (www.magicapp.org) that allows reuse and adaptation.

THE EVIDENCE

A linked systematic review and pairwise meta-analysis (13 trials including 29 614 participants) of benefits and harms associated with SGLT-2 inhibitors in adults with CKD with or without type 2 diabetes informed guidance. Among individuals at very high risk of CKD progression and complications, moderate to high certainty evidence shows SGLT-2 inhibitors (relative to placebo or standard care without SGLT-2 inhibitors) decrease all-cause and cardiovascular mortality, hospitalisation for heart failure, kidney failure, non-fatal myocardial infarction, and non-fatal stroke. Among individuals at high risk, moderate to high certainty evidence shows SGLT-2 inhibitors result in similar benefits across outcomes except demonstrating little or no effect on hospitalisation for heart failure and kidney failure. Among individuals at moderate and low risk, moderate to high certainty evidence shows SGLT-2 inhibitors probably reduce all-cause mortality and non-fatal stroke, with little or no effect for other outcomes of benefit. Risk-stratified estimates were unavailable for outcomes of harm; the panel therefore considered absolute effects summarised across risk strata. SGLT-2 inhibitors are associated with little or no effect on acute kidney injury requiring dialysis, bone fractures, lower limb amputations, ketoacidosis, genital infections, or symptomatic hypovolaemia, although a residual possibility of harms at the individual patient level remains.

UNDERSTANDING THE RECOMMENDATION

In order to apply recommendations, clinicians must appropriately identify adults with CKD, consider the underlying aetiology, and risk stratify them based on glomerular filtration rate (estimated or measured) and degree of albuminuria. In addition, further estimation of a given patient's risk based on the extent of their kidney disease and other comorbidities may be warranted to inform individual-level decisions and shared decision making. Available risk calculators may help estimate a given patient's risk of CKD progression and complications.

Why is the guideline needed?

Chronic kidney disease (CKD) is characterised by abnormalities of kidney structure or function, present for a minimum of three months, and is classified based on aetiology, glomerular filtration rate (GFR), and degree of albuminuria.[1] CKD affects approximately 850 million individuals internationally, is the tenth leading cause of death, and is projected to be the fifth leading cause by 2050.[2-4] Although clinical trajectories vary across individuals, CKD is generally progressive, with declining GFR and progressive albuminuria associated with an increasing risk of cardiovascular complications, kidney failure, and premature death.[5 6]

For a long time, therapies to slow progression of kidney disease and improve long term prognosis of adults living with CKD were lacking. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have emerged—alongside renin-angiotensin system inhibitors, glucagon-like peptide 1 agonists, and non-steroidal mineralocorticoid receptor antagonists—as therapies with potential cardiovascular and kidney protective effects among individuals with type 2 diabetes and CKD.[7] Recently, two randomised trials have demonstrated similar cardiovascular and kidney benefits with the use of SGLT-2 inhibitors among non-diabetic individuals with CKD at varying GFRs and degrees of albuminuria.[8 9]

Previous guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) recommended the use of SGLT-2 inhibitors for patients with type 2 diabetes, CKD, and an estimated GFR of ≥20 mL/min per 1.73 m^2.[10] Their more recent guidance provide recommendations for SGLT-2 inhibitors more broadly for adults with CKD irrespective of diabetes status; however, recommendations are limited to specific risk groups (that is, an estimated GFR ≥20 mL/min per 1.73 m^2 with urine albumin to creatinine ratio (ACR) ≥20 mg/mmol (≥200 mg/g) with concurrent heart failure; or with an estimated GFR 20-45 mL/min per 1.73 m^2 with urine ACR <20 mg/mmol).[11] Moreover, these recommendations are primarily informed by a systematic review and meta-analysis of large double-blind, placebo-controlled trials of at least six months duration evaluating SGLT-2 inhibitors across disease populations including CKD. The review included only four large trials including adults with CKD and did not account for the entirety of existing randomised trial evidence applicable to the CKD population. The review and practice guideline did not take into account treatment effects in absolute terms based on varying prognoses and baseline risks (that is, likelihood of events occurring without treatment), therefore failing to provide risk-stratified interpretations of the evidence and risk-stratified recommendations.[11 12]

We need trustworthy and actionable guidelines that consider all available randomised trial evidence regarding benefits and harms, translate evidence into absolute effects for patient-important outcomes over a reasonable timeframe, and provide risk-stratified recommendations that account for the variable prognoses of adults living with CKD. An international guideline panel involving diverse healthcare professionals, patient partners, and methodologists experienced in guideline development provides the basis for practice guidance that can be used, adapted, and widely implemented.[13]

Context for recommendations

This practice guidance is intended to facilitate evidence-informed decision making for nephrologists, endocrinologists, internal medicine physicians, general practitioners, and patients with established CKD regardless of degree of kidney dysfunction and albuminuria. The recommendations take into account all available evidence regarding SGLT-2 inhibitors for adults with CKD; the expertise and experience of healthcare professionals, researchers, guideline methodologists, and people living with CKD; and the values and preferences of people with CKD when making treatment decisions, informed directly by patient partners on the guideline panel. The recommendations also take into account other factors such as practical issues, affordability, and health equity; follow standards for trustworthy guidelines; and use the GRADE approach.[13 14]

Linked resources in this *BMJ* Rapid Recommendations cluster

Recommendations are informed by a systematic review and meta-analysis evaluating SGLT-2 inhibitors for adults with CKD, including individuals with and without type 2 diabetes. Summary of findings tables included in the guideline are directly informed by the systematic review.

This guideline on SGLT-2 inhibitors for individuals with CKD parallels an ongoing living *BMJ* Rapid Recommendation on drugs for type 2 diabetes, informed by a living systematic review and network meta-analysis. The living diabetes guideline provides recommendations across varying degrees of cardiovascular and kidney risk profiles, and includes recommendations for SGLT-2 inhibitors in individuals with type 2 diabetes. Approaches to risk stratification and recommendations provided are harmonised between the two guidelines by the MAGIC Evidence Ecosystem Foundation (www.magicevidence.org).

This guideline, as well as the parallel living guideline on drugs for diabetes, contribute to the *BMJ* Rapid Recommendations series, focused on providing clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between MAGIC and *The BMJ*.[19] MAGICapp (www.magicapp.org) houses the full version of the guideline, including interactive decision aids, and is accessible across all devices in multilayered formats.[20] Readers can access an interactive version of this guideline with associated evidence summaries and interactive decision aids via MAGICapp (link below).

Linked resouces

- Zou X, Shi Q, Vandvik P, et al. Sodium glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: a systematic review and meta-analysis. *BMJ Med* 2024;3:e001009.
- Agarwal A, Zeng X, Li S, et al. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors for adults with chronic kidney disease: a clinical practice guideline. *BMJ* 2024;386:e080257, doi:10.1136/bmj-2024-080257
- MAGICapp: https://app.magicapp.org/#/guideline/EezrQj

Approach to risk stratification

Risks of death, adverse cardiovascular outcomes, and progression to kidney failure vary across GFRs and degrees of albuminuria. No single prognostic model was identified that accurately risk-stratifies individuals with varying CKD profiles and produces reliable estimates for all prioritised cardiovascular and kidney outcomes and harms. Ultimately, the panel agreed to use the CGA classification, which incorporates underlying cause of CKD (C), GFR (G), and degree of albuminuria (A), initially introduced in 2012 by KDIGO and maintained in its most recent practice guidance.[1 10 11] Data from a United Kingdom-based primary care database of records collected as part of routine care with general practitioners (99 129 patients) informed baseline risks and absolute effects across cardiovascular and kidney outcomes—specifically, all-cause and cardiovascular mortality, hospitalisation for heart failure, non-fatal myocardial infarction, non-fatal stroke, and kidney failure (see "How this guideline was created" below for more details).[15] Absolute effects were estimated over a five year time-frame.

Table 1 summarises the four risk strata, adopting KDIGO's classification system based on GFR and albuminuria categories;

users may refer to reference materials from KDIGO for a visual representation of the risk stratification approach.

Table 1 | Chronic kidney disease (CKD) prognosis classification system used by KDIGO (adopted from the KDIGO 2024 clinical practice guideline for the evaluation and management of CKD[11])

Risk stratum	Definition
Low risk	Normal/high or mildly decreased GFR (≥60 mL/min per 1.73 m2) with normal or mildly increased albuminuria (<3 mg/mmol)
Moderate risk	Either of: • Normal/high or mildly decreased GFR (≥60 mL/min per 1.73 m2) with moderately increased albuminuria (3-30 mg/mmol) • Mildly to moderately decreased GFR (45 to 59 mL/min per 1.73 m2) with normal or mildly increased albuminuria (<3 mg/mmol)
High risk	Any of: • Normal/high or mildly decreased GFR (≥60 mL/min per 1.73 m2) with severely increased albuminuria (>30 mg/mmol) • Mildly to moderately decreased GFR (45 to 59 mL/min per 1.73 m2) with moderately increased albuminuria (3-30 mg/mmol) • Moderately to severely decreased GFR (30 to 44 mL/min per 1.73 m2) with normal or mildly increased albuminuria (<3 mg/mmol)
Very high risk	Any of: • Mild to moderately (45 to 59 mL/min per 1.73 m2) or moderately to severely decreased GFR (30 to 44 mL/min per 1.73 m2) with severely increased albuminuria (>30 mg/mmol) • Moderately or severely decreased GFR (30 to 44 mL/min per 1.73 m2) with moderately increased albuminuria (3-30 mg/mmol) • Severely decreased GFR or kidney failure (<30 mL/min per 1.73 m2)* with any degree of albuminuria

* SGLT-2 inhibitors should generally not be newly initiated with GFR <20 mL/min per 1.73 m2, though they may be continued even if GFR drops below this threshold for individuals already on therapy (until dialysis initiation).

Beyond accounting for GFR and degree of albuminuria, risk needs to be further stratified in order to tailor care to a given individual. To accomplish this, clinicians may choose to consider other comorbidities, and may use one of several available prognostic models (see appendix).

Applicability of recommendations

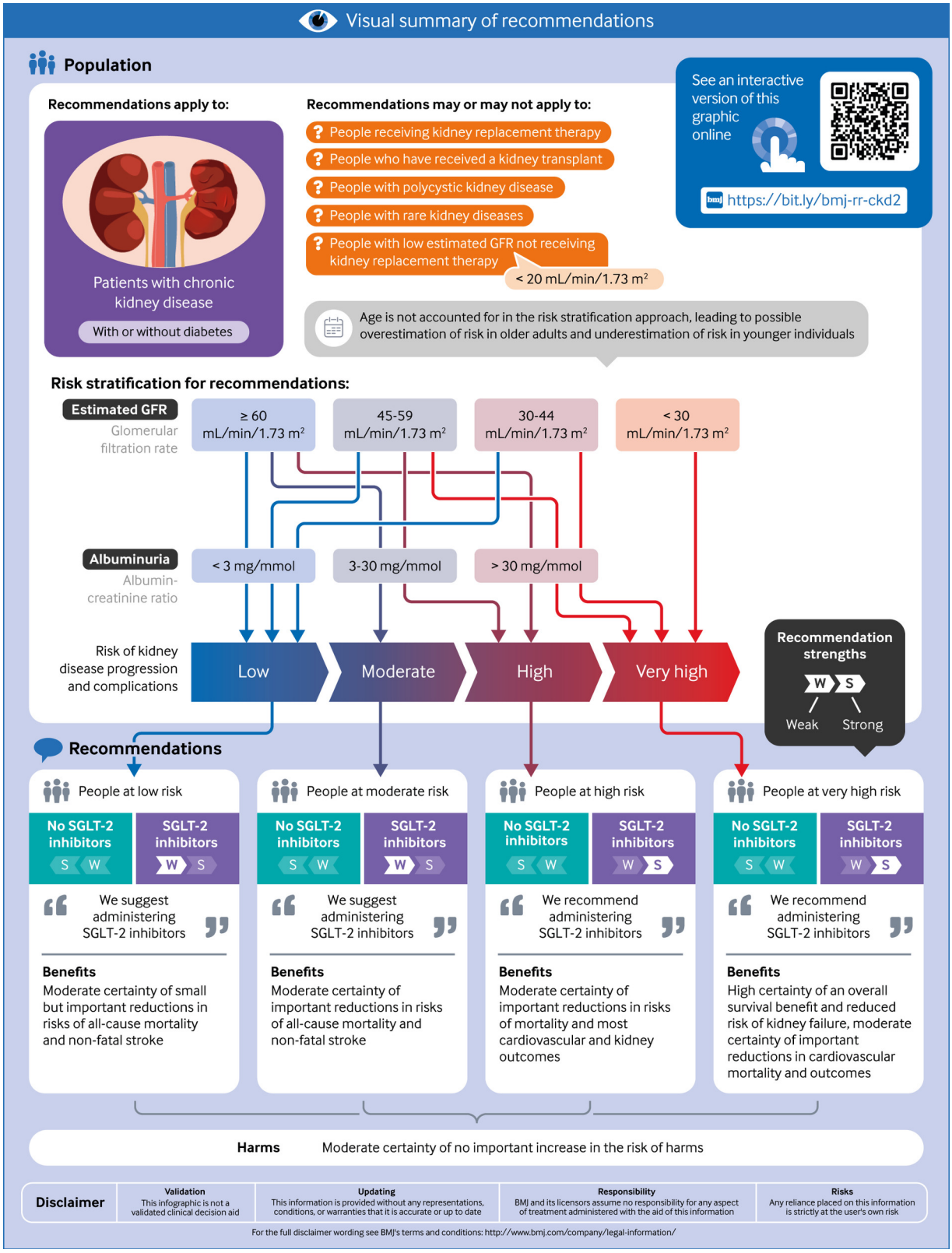
Recommendations apply to most adults with established CKD irrespective of type 2 diabetes status, heart failure status, sex, gender, or ethnicity. In line with internationally accepted definitions, CKD is defined as abnormalities in kidney structure or function for a minimum of three months, with health implications. Either decreased GFR (<60 mL/min per 1.73 m^2) or one or more markers of kidney damage (such as albuminuria with an albumin to creatinine ratio ≥3 mg/mmol) must be present to establish the diagnosis. This guideline does not apply to adults meeting neither criterion and therefore not having CKD.

Recommendations may not be applicable to certain other groups based on specific clinical considerations and lack of representation in included studies:

- Individuals receiving kidney replacement therapy
- Individuals who have received a kidney transplant
- Individuals with polycystic kidney disease
- Individuals with rare kidney diseases
- Individuals with estimated GFR <20 mL/min per 1.73 m^2 and not receiving kidney replacement therapy.

Age is not accounted for in the definition and classification system published by KDIGO in 2012 and maintained in its most recent practice guidelines. This may result in possible overestimation of risk in older adults (such as ≥65 years) and underestimation of risk in younger individuals (such as <40 years),[16] making recommendations less applicable to these groups.

Moreover, individuals with rare kidney diseases (encompassing over 150 conditions as defined by KDIGO) can have higher rates of kidney failure but higher rates of survival relative to the general population of adults with CKD. Evidence regarding SGLT-2 inhibitors in such cases is either low certainty or non-existent. Recommendations may therefore be less applicable to these individuals.[17]



How this guideline was created

Standards, methods, and processes for trustworthy guidance

This *BMJ Rapid Recommendation* was developed in accordance with standards for trustworthy guidance from the Institute of Medicine,[13] and strives to meet criteria for methodological rigour as per AGREE-II.[21]

Who was involved?

We recruited an international guideline panel including patient partners (individuals living with CKD irrespective of disease stage and with or without a history of cardiovascular and kidney complications), general practitioners, internal medicine physicians, endocrinologists, nephrologists, and methodologists. Panel members were diverse in

geography, sex, and expertise. The panel collectively determined the scope of this guideline and formulated recommendations. Methods and clinical co-chairs were selected by the MAGIC Evidence Ecosystem Foundation to lead panel deliberations.

No panel member reported financial conflicts of interest. Intellectual conflicts of interest were minimised and managed in accordance with established policies for *The BMJ* and MAGIC.

What research did the guideline panel request and review?

The panel defined the clinical question and related population, intervention, outcomes and subgroups of interest to be addressed by the guideline. To fully address the specified question, an independent team of clinical epidemiologists, clinical experts, and biostatisticians conducted a pairwise systematic review to examine benefits and harms addressing the clinical question. Team members had expertise in GRADE methods.[14]

A second independent team of epidemiologists, clinical experts, and biostatisticians conducted a review of existing literature to identify prognostic models and classification systems to guide risk stratification of adults across different degrees of CKD severity. Identified prognostic models and classifications were reviewed by a core team of methodologists, and informed the strategy used for risk stratification in the guideline.

The panel did not prioritise a separate systematic review on the values and preferences of adults with CKD and instead relied on input from patient partners and clinical experts on the panel to inform their judgments.

What outcomes did the guideline panel request and review?

Twelve patient-important outcomes were selected in the systematic review summarising benefits and harms of SGLT-2 inhibitor therapy. Panel members completed a survey to prioritise these outcomes from the perspective of an average adult with CKD.

The following outcomes were deemed as being of critical importance (rated 7 to 9 on a 9-point ordinal scale): all-cause mortality, cardiovascular mortality, kidney failure, non-fatal stroke, hospitalisation for heart failure, non-fatal myocardial infarction, acute kidney injury requiring dialysis, and lower limb amputation.

The following outcomes were deemed as being of importance (rated as 4 to 6 on the scale): ketoacidosis, bone fracture, genital infection, and symptomatic hypovolaemia.

All 12 outcomes—six addressing benefit and six addressing harm (adverse events)—were retained as being patient-important.

How did the panel formulate recommendations?

Pre-established standards, methods, and processes for the *BMJ* Rapid Recommendations for developing trustworthy guidelines were adopted.[19 20] The GRADE approach provided the framework for evaluating certainty of available evidence and determining the strength and direction of recommendations. With GRADE, recommendations can be strong or weak, and for or against a treatment or course of action.[14]

To facilitate panel deliberations regarding interpretation of effects associated with SGLT-2 inhibitors, a survey was conducted asking panel members to rate the relative importance to patients of identified outcomes on an ordinal scale from 1 (not patient-important) to 9 (of critical importance).

The panel adopted a consensus based approach to establish thresholds for minimal important differences for each prioritised outcome. The minimal important difference is the smallest treatment effect that a patient would deem as being important. Established thresholds facilitated interpretation of absolute effects (differentiating important from unimportant (that is, little or no difference) effects) and directly influenced ratings of precision when evaluating certainty of evidence using GRADE. Thresholds were generally inversely proportional to the relative patient importance of outcomes (that is, more patient-important outcomes were assigned lower thresholds whereby a treatment effect was deemed important). The minimal important difference thresholds used are summarised in the Summary of Findings tables provided in MAGICapp and in the linked systematic review and meta-analysis.

Panel meetings were facilitated by methods and clinical co-chairs, and were conducted in July 2023 via web conference. The panel reviewed survey results regarding outcome prioritisation; reached agreement regarding an approach to risk stratification, patient values and preferences, and minimal important difference thresholds for interpreting treatment effects in absolute terms; and reviewed Summary of Findings tables, providing risk-stratified summaries of evidence across prioritised outcomes and their respective certainty ratings. A consensus based approach was adopted to move from evidence to recommendations, with informal voting used to anchor discussions and facilitate consensus. When the panel was unable to reach a consensus by discussion, a priori voting rules were established; voting was limited to panel members with clinical expertise and patient partners, excluding methodologists.

In addition to consideration of absolute benefits and harms for prioritised patient-important outcomes and associated certainty of the evidence, several other factors were considered in moving from evidence to recommendations. Decisional domains included values and preferences of individuals living with CKD, feasibility, and acceptability. Issues related to equity were discussed but did not weigh heavily on deliberations when making recommendations. The panel also provided input regarding practicalities of administering SGLT-2 inhibitors, and issues related to applicability of recommendations to specific groups.

Guidance was drafted by the methods chair with input from the clinical chair and methods trainee co-chair, and was circulated for review to the panel. Internal feedback was incorporated, and the panel approved the final version of the guidance prior to submission.

What is the approach to prognosis and risk prediction for outcomes?

The methods team conducted a review of existing prognostic models for risk stratification of individuals with CKD and establishing risk-stratified prognoses (that is, baseline risks) for cardiovascular and kidney outcomes. Evaluation of identified prognostic models, including those reported by the CKD Prognosis Consortium, yielded no models that provided accurate risk stratification (that is, adequate discrimination and calibration) across the majority of prioritised cardiovascular and kidney outcomes.

The KDIGO classification was considered as an alternate approach to risk stratification of individuals with CKD based on a combined assessment of GFR (measured or estimated) and albuminuria levels.[1] This classification system was adopted due to its widespread use and practicality of application in clinical practice, requiring only GFR and albuminuria inputs to estimate risk. Data from a large retrospective cohort study including a primary care database—the United Kingdom Clinical Practice Research Datalink (CPRD)—was used to inform baseline risks and absolute effects across cardiovascular and kidney outcomes using this classification. The United Kingdom CPRD uses medical records collected as part of routine care with general practitioners, and was deemed appropriately representative of a community based population with CKD. Data were used to inform risk-stratified estimates for all-cause and cardiovascular mortality, hospitalisation for heart failure, non-fatal myocardial infarction, non-fatal stroke, and kidney failure.[15] Absolute effects were estimated over a five year time-frame for all outcomes.

The methods team and panel acknowledged several limitations with adopting the KDIGO classification for risk stratification. The classification uses fixed thresholds for GFR and albuminuria without stratifying for age. Among younger individuals, a small GFR decline with or without albuminuria may represent pathological CKD with a higher risk of mortality and cardiovascular and kidney-related sequelae. On the contrary, among older individuals, an isolated decline in GFR may represent a physiological process without similar increases in these risks.[16] Therefore, universal thresholds for both variables could lead to a misleading incidence of CKD without proportionally increased or decreased risks of kidney failure and mortality, and with a risk of underestimating risk in younger individuals and overestimating it in older individuals.[16] The panel also noted issues related to GFR being either estimated or measured in the classification system and that different equations may be used to estimate GFR.

The panel acknowledged that, although risk stratification was made possible for outcomes of benefit with this strategy, harm outcomes were not able to be similarly risk-stratified. Treatment effects were anticipated to be similar irrespective of baseline kidney function.[22] However, possible

variation in baseline risks of harms across risk strata was anticipated (such as higher risk CKD groups are at higher risk of developing acute kidney injury). Certainty in evidence was therefore downgraded for indirectness in baseline risks to reflect the uncertainty in using the unstratified absolute effect estimates for these outcomes to inform decision making.

How were values and preferences of patients incorporated?

In the absence of a systematic review regarding the values and preferences of adults with CKD as they apply to SGLT-2 inhibitors, the panel relied on their own judgments of what well informed adults would value after carefully balancing benefits, harms, and burdens of therapy. Input from three patient partners who live with CKD informed judgments. The following values and preferences were deemed to be typical of well informed adults with CKD:

- Most adults living with CKD would be inclined to accept SGLT-2 inhibitor therapy when faced with moderate or high certainty of potential benefit and moderate or high certainty of little or no increased risk of harms. The larger the benefit, the more individuals would be willing to accept therapy.
- Most adults living with CKD would be disinclined to accept SGLT-2 inhibitor when faced with moderate or high certainty of little or no benefit regardless of associated harms.

Even when faced with moderate or high certainty of unimportant harms, there remains a possibility for harm that may drive individuals to avoid therapy unless benefits are compelling. Moreover, the introduction of an additional medication for individuals who may already be taking numerous medications (increased pill burden) may be considered an important harm. These considerations were incorporated when making recommendations.

The recommendations

Recommendations across risk strata were informed by 13 randomised trials including 29 614 participants.

Recommendation 1: For adults at low risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)

Understanding the recommendation—Moderate certainty of small but important reductions in risks of all-cause mortality and non-fatal stroke, balanced against moderate certainty of no important increase in the risk of harms, led to a weak recommendation in favour of treatment. The panel deliberated on whether treatment effects justified a weak recommendation in favour or against—given that benefits are more marginal than in higher risk groups and there remains a possibility of adverse events at the individual level (even in the absence of an important increase in risk per 1000 individuals)—and ultimately concluded that most patients would be inclined to accept treatment.

Benefits and harms—In adults at low risk, SGLT-2 inhibitors probably decrease all-cause mortality (7 fewer per 1000 adults, 95% confidence interval 11 fewer to 1 fewer) and non-fatal stroke (10 fewer per 1000, 16 fewer to 2 fewer) (both moderate certainty) with little or no effect on cardiovascular mortality, hospitalisation for heart failure, kidney failure, and non-fatal myocardial infarction (all moderate to high certainty). Therapy is probably associated with little or no increased risk of harms, including acute kidney injury requiring dialysis (9 fewer per 1000, 14 fewer to 1 fewer), bone fracture (2 more per 1000, 10 fewer to 15 more), lower limb amputation (2 more per 1000, 4 fewer to 10 more), ketoacidosis (4 more per 1000, 1 more to 9 more), genital infection (27 more per 1000, 17 more to 39 more), and symptomatic hypovolaemia (32 more per 1000, 17 more to 49 more) (low certainty for lower limb amputation; moderate certainty for all other outcomes). Despite no effect estimates crossing the pre-established thresholds for minimal important differences across harm outcomes, the panel acknowledged adverse events remained plausible at the individual patient level.

Values and preferences—Applying the values and preferences agreed on by the panel with patient partner input (see "How this guideline was created"), the majority of individuals would be expected to accept SGLT-2 inhibitors, though a reasonable proportion would likely decline, given the marginal benefits, increased pill burden, medication costs, and a residual possibility of harms.

Recommendation 2: For adults at moderate risk of CKD progression and complications, we suggest administering SGLT-2 inhibitors (weak recommendation in favour)

Understanding the recommendation—Moderate certainty of important reductions in risks of all-cause mortality and non-fatal stroke, balanced against moderate certainty of no important increase in the risk of harms, justified a weak recommendation in favour.

Benefits and harms—In adults at moderate risk, SGLT-2 inhibitors probably decrease all-cause mortality (13 fewer per 1000, 95% CI 22 fewer to 2 fewer) and non-fatal stroke (13 fewer per 1000, 21 fewer to 3 fewer) (both moderate certainty), with little or no effect on cardiovascular mortality, non-fatal myocardial infarction (both moderate certainty), hospitalisation for heart failure, and kidney failure (both high certainty). Harms are the same as for adults in other risk strata, acknowledging uncertainty given lack of risk-stratified estimates and the residual possibility of adverse events at the individual patient level.

Values and preferences—Same as for recommendation 1.

Recommendation 3: For adults at high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)

Understanding the recommendation—Moderate certainty of important reductions in risks of mortality and most cardiovascular and kidney outcomes, combined with moderate certainty of no important increase in the risk of harms, motivated a strong recommendation in favour of treatment.

Benefits and harms—In individuals at high risk, SGLT-2 inhibitors probably decrease all-cause mortality (24 fewer per 1000, 95% CI 41 fewer to 3 fewer) and cardiovascular mortality (6 fewer per 1000, 10 fewer to 1 fewer), non-fatal myocardial infarction (21 fewer per 1000, 34 fewer to 6 fewer), and non-fatal stroke (21 fewer per 1000, 34 fewer to 5 fewer) (all moderate certainty), with little or no effect on hospitalisation for heart failure and kidney failure (both high certainty). Harms are the same as for adults in other risk strata, acknowledging uncertainty given lack of risk-stratified estimates and the residual possibility of adverse events at the individual patient level.

Values and preferences—Applying the values and preferences agreed on by the panel with patient partner input (see "How this guideline was created"), the panel inferred that all or almost all individuals would be inclined to receive SGLT-2 inhibitors in light of benefits substantially outweighing potential harms and treatment burdens, and did not anticipate substantial variability in preferences.

Recommendation 4: For adults at very high risk of CKD progression and complications, we recommend administering SGLT-2 inhibitors (strong recommendation in favour)

Understanding the recommendation—High certainty of an overall survival benefit and reduced risk of kidney failure, moderate certainty of important reductions in cardiovascular mortality and

outcomes, and moderate certainty of no important increase in the risk of harms, justified a strong recommendation in favour.

Benefits and harms—In individuals at very high risk, SGLT-2 inhibitors decrease all-cause mortality (48 fewer per 1000, 95% CI 84 fewer to 6 fewer) and kidney failure (58 fewer per 1000, 72 fewer to 42 fewer) (both high certainty), and probably decrease cardiovascular mortality (10 fewer per 1000, 17 fewer to 3 fewer), hospitalisation for heart failure (25 fewer per 1000, 32 fewer to 17 fewer), non-fatal myocardial infarction (32 fewer per 1000, 51 fewer to 9 fewer), and non-fatal stroke (25 fewer per 1000, 40 fewer to 6 fewer) (all moderate certainty). Harms are the same as for adults in other risk strata, acknowledging uncertainty given lack of risk-stratified estimates and the residual possibility of adverse events at the individual patient level.

Values and preferences—Same as recommendation 3.

Resource, equity, acceptability, and feasibility considerations

SGLT-2 inhibitors are widely available internationally.[23] Most SGLT-2 inhibitors are available as once-daily oral regimens. Individuals initiating SGLT-2 inhibitors require counselling regarding possibility of adverse events and sick day rules,[24 25] but otherwise do not require intensive follow-up. These considerations are applicable across risk strata.

Practical considerations

- The following should be considered when prescribing SGLT-2 inhibitors to adults with CKD:
  - SGLT-2 inhibitors may be initiated at the highest possible dose and do not require dose titration
  - SGLT-2 inhibitors may be initiated in adults with estimated glomerular filtration rate (GFR) ≥20 mL/min per 1.73 m^2
  - Once initiated, SGLT-2 inhibitors may be continued even if estimated GFR <20 mL/min per 1.73 m^2 until dialysis initiation
  - SGLT-2 inhibitors are likely to cause an acute transient decline in GFR within two to four weeks after initiation. However, it is not routinely necessary to check blood tests after initiating an SGLT-2 inhibitor in adults with CKD, except in high risk individuals such as those with prior acute kidney injury or at risk of volume depletion
  - A transient decline in GFR should not be a reason to discontinue therapy unless it exceeds 25% from baseline. If treatment is discontinued, another attempt to initiate therapy may be pursued after recovery of kidney function
  - Individuals who are taking diuretics at baseline or are otherwise at risk of volume depletion may require closer monitoring and diuretic titration when initiating SGLT-2 inhibitors. This may be particularly pertinent with exposure to hot weather
  - In individuals with concomitant heart failure, SGLT-2 inhibitors should be initiated irrespective of kidney function and degree of albuminuria
- Individuals should be counselled regarding the following:
  - Potential adverse events, including genital mycotic infections, acute kidney injury, fractures, euglycaemic ketoacidosis, volume depletion, Fournier's gangrene, and amputations. Even for harm outcomes where important increases in risk are not evident, a residual risk of such events exists and warrants counselling
  - The need to stop medication if unwell, engaging in prolonged fasting, undergoing surgery, or experiencing severe gastrointestinal losses such as diarrhoea or vomiting (that is, sick day counselling).

The beneficial effects of SGLT-2 inhibitors are considered to be class effects. By extension, all SGLT-2 inhibitors are considered similarly.

SGLT-2 inhibitors that may be considered for use in individuals with CKD include canagliflozin, dapagliflozin, and empagliflozin.

Key uncertainties and future directions

We identified the following key uncertainties and areas for future research:

- Development of a prognostic model that estimates cardiovascular and kidney risk in adults with CKD (currently available models either do not provide accurate risk stratification or do not do so for the majority of key outcomes)
- Risk estimation for patient-important outcomes that incorporates age stratification (not currently incorporated into the KDIGO classification based on GFR and albuminuria)
- Risk-stratified estimates for patient-important harm outcomes (no robust evidence currently available to inform baseline risks across different risk strata)
- Safety of initiating SGLT-2 inhibitors with a baseline GFR <20 mL/min per 1.73 m^2 (current evidence and guidance are less applicable to this group)
- Impact of initiating SGLT-2 inhibitors among adults receiving kidney replacement therapy (peritoneal or haemodialysis) or after kidney transplantation (current evidence and guidance are less applicable to these groups)
- Impact of continuing SGLT-2 inhibitors with low GFRs (particularly <20 mL/min per 1.73 m^2) or for adults who begin kidney replacement therapy (current evidence and guidance are more uncertain for or less applicable to these groups)
- Impact of initiating SGLT-2 inhibitors for adults with rare kidney diseases, particularly autosomal dominant polycystic kidney disease (current evidence and guidance are less applicable to these groups)
- Impact of initiating SGLT-2 inhibitors for adults with other diseases in which kidney disease is often implicated, such as antineutrophil cytoplasmic antibody (ANCA) associated vasculitis and lupus nephritis (current evidence and guidance are less applicable to these groups)[18]
- Evidence of values and preferences of adults with CKD regarding use of SGLT-2 inhibitors as it applies to different risk strata (more robust evidence incorporating input from a larger cohort of adults living with CKD is warranted).

How patients were involved in the creation of this article

The panel included three patients with CKD. Their perspectives informed judgments regarding values and preferences associated with decision-making related to SGLT-2 inhibitors.

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Main infographic: Summary of recommendations and evidence

Appendix: Summary of prognostic models