Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence

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The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD) represents a focused update of the KDIGO 2020 guideline on the topic. The guideline targets a broad audience of clinicians treating people with diabetes and CKD. Topic areas for which recommendations are updated based on new evidence include Chapter 1: Comprehensive care in patients with diabetes and CKD and Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD. The content of previous chapters on Glycemic monitoring and targets in patients with diabetes and CKD (Chapter 2), Lifestyle interventions in patients with diabetes and CKD (Chapter 3), and Approaches to management of patients with diabetes and CKD (Chapter 5) has been deemed current and was not changed. This guideline update was developed according to an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies and appraisal of the quality of the evidence, and the strength of recommendations followed the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed, and areas for which additional research is needed are presented.

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The KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD) follows only 2 years after the original 2020 Clinical

Practice Guideline[1] on this topic. The update was motivated by the wealth of high-quality new evidence that has quickly become available since the original 2020 guideline was published and calls from the community to help guide application of these new data. The short interval between guidelines reflects the rapid pace of advances in the management of diabetes and CKD.

The scope of the 2022 guideline is unchanged from 2020. The guideline addresses both type 1 diabetes (T1D) and type 2 diabetes (T2D), all stages of CKD (defined as persistent albuminuria [albumin–creatinine ratio {ACR} ≥30 mg/g {≥3 mg/mmol}], persistently reduced estimated glomerular filtration rate [eGFR <60 ml/min per 1.73 m^2], or both), patients with a kidney transplant, and patients treated with hemodialysis or peritoneal dialysis. Lifestyle, pharmacologic, self-care, and systems interventions were all evaluated. The guideline focuses on clinical management questions that can be addressed with high-quality scientific evidence, specifically, randomized controlled trials (RCTs) that evaluated clinically relevant outcomes.

The Evidence Review Team (ERT) first updated the systematic literature search for each topic covered by the 2020 guideline. The Work Group reviewed the ERT summary of new studies and judged by topic whether there was sufficient new evidence to conduct a full quantitative reassessment with reconsideration of recommendations. For these topics, the ERT updated the evidence synthesis (both narrative and quantitative) and reassessed the grading for the quality of the evidence base, and the Work Group revised the corresponding guideline chapters accordingly.

Based on this updated review, Chapters 1 (Comprehensive care) and 4 (Glucose-lowering therapies) were substantially revised. These include full revisions for the use of sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA), and the development of a new section on mineralocorticoid receptor antagonists (MRA). Chapters 2 (Glycemic monitoring and targets in patients with diabetes and CKD), 3 (Lifestyle interventions in patients with diabetes and CKD), and 5 (Approaches to management of patients with diabetes and CKD) were deemed current, and no changes were made to recommendations or practice points. For a detailed list of the changes between the 2020 and 2022 guidelines, please see Supplementary Table S1.

Recommendations were graded using the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) criteria.[2] In addition, ungraded practice points were issued to provide guidance and context for implementation of recommendations or when expert guidance was deemed necessary, but available evidence was insufficient for a formal recommendation.

Comprehensive care

People with diabetes and CKD are at high risk for progression to kidney failure and cardiovascular events (myocardial infarction [MI], stroke, ischemia, arrhythmia, and heart failure), as well as acute diabetes-related complications (hypoglycemia and diabetic ketoacidosis) and other long-term diabetes complications (retinopathy, neuropathy, foot ulcers, and amputations). Like the 2020 guideline, the 2022 guideline advocates a comprehensive approach to assess the multiple risk factors for these adverse outcomes and partnership with patients and healthcare systems to implement evidence-based therapies. Such multifactorial care has been shown to improve outcomes in RCTs.[3–6]

A pyramid graphic that summarizes components of comprehensive care of patients with diabetes and CKD has been updated to reflect new recommendations (Figure 1). The graphic has been rearranged to reflect that drugs proven to improve kidney and cardiovascular outcomes are part of a foundation of care that, along with lifestyle, aims to improve clinical outcomes irrespective of effects on intermediate targets. For example, SGLT2i are first-line therapy for people with T2D and CKD regardless of glycemia, but SGLT2i also lower blood glucose. Therefore, SGLT2i are considered a foundation of pharmacologic therapy for T2D and CKD, with additional agents layered on top of SGLT2i and metformin as needed to attain individualized glycemic targets (Figure 2).

When designing patient-centered treatment regimens, we suggest that patients and healthcare professionals build from the base of the pyramid upward. Repeat evaluations at regular intervals are needed to ensure that interventions are titrated appropriately and combinations of interventions are prescribed to optimize care. In partnership with the American Diabetes Association (ADA), a corresponding flow diagram was also generated to demonstrate this approach in a top-down configuration (Figure 3). The flow diagram shows that multiple aspects of care should be addressed in parallel, advanced over time through longitudinal evaluations, and refreshed through repeat risk assessments. Regular screening for CKD with assessment of ACR and eGFR was stressed as being a critical prerequisite for correct diagnosis of CKD and implementation of interventions.[7]

SGLT-2 inhibitors

Seven large clinical outcomes trials of SGLT2i were published between release of the 2020 guideline and the development of the 2022 guideline update.[8–14] These trials provide high-quality data on the benefits and harms of this class of medications, as detailed in the full guideline document, and reinforce the strong recommendation offered in 2020 that patients with T2D and CKD be treated with an SGLT2i across albuminuria and most eGFR categories (Grade 1A).

An important modification is the lower eGFR threshold at which SGLT2i should be initiated. The 2022 guideline advocates initiating an SGLT2i for patients with T2D and CKD who have an eGFR ≥20 ml/min per 1.73 m^2 (Figures 2 and 3), as opposed to ≥30 ml/min per 1.73 m^2 in the 2020 guideline. Patients with T2D, CKD, and eGFR ≥20 ml/min per 1.73 m^2 have now been

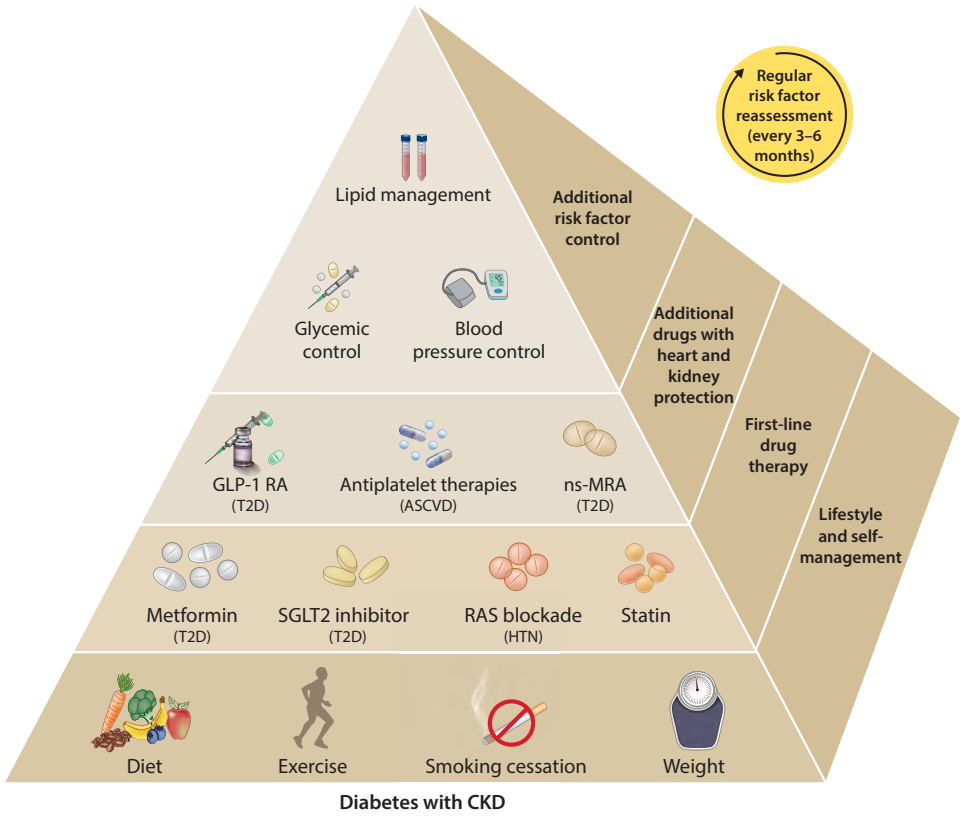

Figure 1 | Kidney–heart risk factor management. People with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive approach to improve kidney and cardiovascular outcomes. This approach should include a foundation of lifestyle modification and self-management for all patients,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

extensively studied in RCTs of SGLT2i. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trials enrolled CKD patients with eGFR down to as low as 25 ml/min per 1.73 m^2.[9,12] The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) and The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trials, although not conducted exclusively in CKD populations, enrolled participants with eGFR as low as 20 ml/min per 1.73 m^2.[8,14] The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY), which enrolled an exclusive CKD population and was stopped early for benefit, also enrolled participants with eGFR ≥20 ml/min per 1.73 m^2.[15] Subgroup analyses of individual trials and meta-analyses have consistently demonstrated kidney and cardiovascular benefits across eGFR categories, including participants with eGFR <30 ml/min per 1.73 m^2 and participants without albuminuria.[16,17] Several trial protocols specified continuation of the study drug if eGFR fell below the eGFR threshold required for eligibility; observed benefits with this approach further support use of SGLT2i at lower eGFR and were the basis for a revised practice point (Practice Point 1.3.6) advocating that SGLT2i be continued as long as tolerated, even if eGFR falls below 20 ml/min per 1.73 m^2, until kidney replacement therapy is initiated.

The 2022 guideline more firmly emphasizes that SGLT2i should be used for patients with T2D and CKD, regardless of glycemia. Multiple SGLT2i trials included subsets of participants without diabetes, who appear to have derived similar benefits as those with T2D,[8,14,18] and increasing evidence supports non-glycemic mechanisms of kidney and cardiovascular benefits.

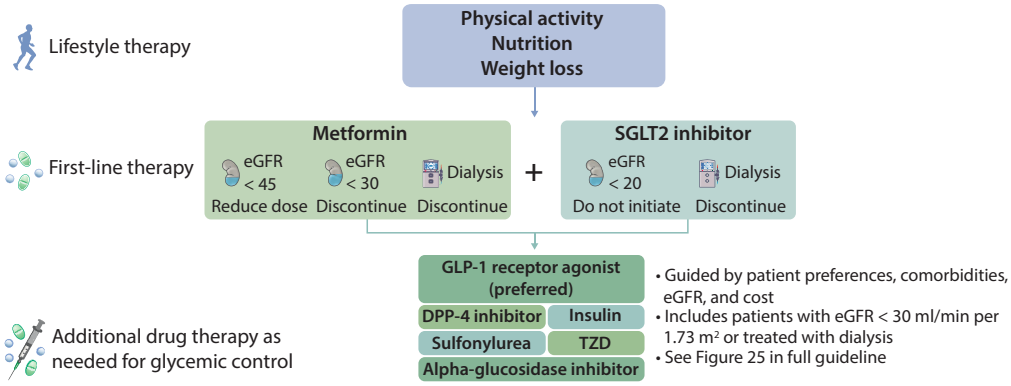

Figure 2 | Treatment algorithm for selecting glucose-lowering drugs for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. DPP-4, dipeptidyl peptidase-4;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

SGLT2i have been demonstrated to be effective and safe at any level of glycemic control and with or without concomitant use of renin–angiotensin system inhibitors (RASi) or metformin. To reinforce these principles, SGLT2i were moved from Chapter 4 (Glucose-lowering therapies) to Chapter 1 (Comprehensive care). Combinations of SGLT2i with other drugs are addressed in practice points and in Chapter 4 (Table 1 and Figure 4[19]).

Unfortunately, data remain insufficient to make a recommendation on SGLT2i use for people with T1D and CKD, kidney transplant recipients, or patients treated with dialysis. These populations remain excluded from the SGLT2i recommendation, and the need for rigorous studies in these populations is highlighted in research recommendations.

GLP-1 receptor agonists

One new trial (Effect of Efpeglenatide on Cardiovascular Outcomes [AMPLITUDE-O][20]) strengthened evidence for cardiovascular benefits of GLP-1 RA and bolstered the hypothesis that GLP-1 RA may also improve kidney outcomes. Proven cardiovascular benefits of GLP-1 RA have been demonstrated across strata of eGFR and serve as the major rationale for recommending GLP-1 RA as the preferred glucose-lowering drug for people with T2D and CKD who were not attaining glycemic goals despite use of SGLT2i and metformin (or who were unable to use SGLT2i and/or metformin). Therefore, GLP-1 RA remain the recommended second-line drug class for glucose-lowering in T2D and CKD (Figures 2 and 3).

The quality of supporting evidence for the use of GLP-1 RA continues to be rated as B because dedicated trials in populations with CKD have not yet been published (indirectness). The recommendation has a Level 1 strength of recommendation because the Work Group judged that most people with T2D and CKD who need an additional drug therapy to control blood glucose (after lifestyle modification and use of SGLT2i and metformin, if appropriate and tolerated) would choose a GLP-1 RA over other glucose-lowering drugs. For this particular application, the demonstrated cardiovascular and possible kidney benefits of GLP-1 RA offer clear benefits to alternative drugs. The recommendation does not call for use of GLP-1 RA among patients with T2D who have achieved their target glycemic control with lifestyle, SGLT2i, and metformin, based on currently available data on GLP-1 RA risks and benefits.

GLP-1 RA were also demonstrated to effectively reduce weight.[21–24] Weight loss is an important goal of some obese patients with CKD, including those who want to lose weight to facilitate a kidney transplant. The Work Group found insufficient evidence to recommend use of GLP-1 RA for weight loss among people with diabetes and CKD specifically, but issued a new practice point highlighting the potential advantages of this approach (Table 1).

Non-steroidal mineralocorticoid antagonists

Two large clinical trials (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease [FIDELIO-DKD][25] and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease [FIGARO-DKD][26]) and a pre-specified individual-level combined analysis of these 2 trials (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis [FIDELITY][27]) evaluated the benefits and risks of a new non-steroidal MRA (ns-MRA), finerenone. FIDELIO-DKD and FIGARO-DKD each enrolled people with T2D treated with the maximum-tolerated dose of RASi who had residual albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]) and a non-elevated serum potassium (<4.8 mEq/l at screening). Together, 67% had severe albuminuria (ACR ≥300 mg/g [≥30 mg/mmol]), and mean eGFR was 57.6 ml/min per 1.73 m^2.[27] Participants were randomly assigned to finerenone or placebo.

In FIDELIO-DKD, finerenone significantly reduced the incidence of both the primary composite kidney outcome (kidney failure, sustained decrease ≥40% in eGFR, or death from kidney causes; hazard ratio [HR]: 0.82, 95% confidence interval [CI]: 0.73–0.93) and the secondary composite cardiovascular outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart

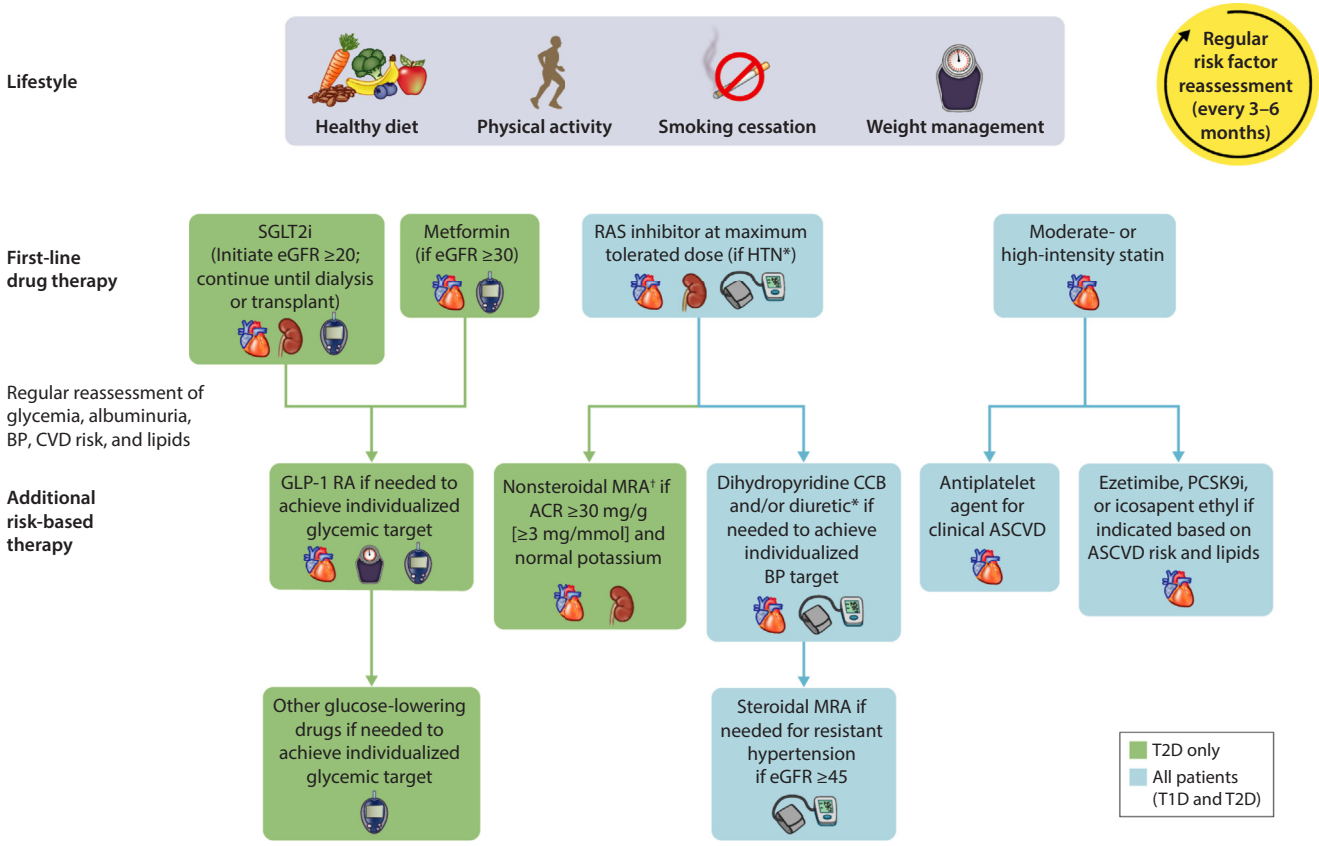

Figure 3 | Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease. *Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) should be first-line therapy for hypertension (HTN) when albuminuria is present, otherwise dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all 3 classes are often needed to attain blood pressure (BP) targets. †Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist (MRA) with proven clinical kidney and cardiovascular benefits. Icons presented indicate the following benefits: blood pressure cuff = blood pressure–lowering; glucometer = glucose-lowering; heart = heart protection; kidney = kidney protection; scale = weight management; ACR, albumin–creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin–angiotensin system; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

failure; HR: 0.86, 95% CI: 0.75–0.99).[25] In FIGARO-DKD, finerenone significantly reduced the composite cardiovascular outcome, which was the primary outcome of the trial (HR: 0.87, 95% CI: 0.76–0.98).[26] In FIDELITY, the cardiovascular composite was reduced in those treated with finerenone (HR: 0.86; 95% CI: 0.78–0.95), without significant heterogeneity according to any reported baseline characteristic.[27] There was also a lower incidence of the kidney composite of kidney failure, >57% decrease in eGFR, or death from kidney causes among those treated with finerenone (HR: 0.77; 95% CI: 0.67–0.88), and a lower incidence of kidney failure, defined as initiation of chronic dialysis or kidney transplantation (HR: 0.80; 95% CI: 0.64–0.99). Hyperkalemia was more common with finerenone compared with placebo (14% vs. 6.9%), with a small cumulative incidence of permanent discontinuation of study drug for hyperkalemia (1.7% vs. 0.6%) and no deaths due to hyperkalemia over 3 years.[27]

Esaxerenone, another ns-MRA, has also been shown to lower urinary albumin excretion. However, the long-term kidney and cardiovascular benefits of esaxerenone have not been established, and regulatory approval for esaxerenone is, so far, limited to treatment of hypertension in Japan.[28,29]

The Work Group judged that the majority of well-informed patients with T2D who had persistent albuminuria (ACR >30 mg/g [>3 mg/mmol]) and non-elevated serum potassium despite maximal tolerated dose of RASi would choose to receive an ns-MRA with proven kidney and cardiovascular protective benefits (Table 1). This recommendation is based on the high-quality evidence from FIDELIO-DKD and FIGARO-DKD (Grade A, summarized above) that finerenone slows progression of CKD and reduces risks of cardiovascular events in this population.[25,26] Nonetheless, some patients will choose not to be treated with an ns-MRA because of lack of definitive data on benefits and risks when an ns-MRA is added to an SGLT2i (which is part of the current standard of care), modest representation of patients with certain relevant characteristics (e.g., moderate albuminuria) in the FIDELIO-DKD and FIGARO-DKD trials,

Table 1 | Select recommendations and practice points from the Kidney Disease: Improving Global Outcomes 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD)

Comprehensive care
Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.
SGLT2 inhibitors
Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).
Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen.
Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.
Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).
Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.
Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.
Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.
Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).
Mineralocorticoid receptor antagonists
Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).
Practice Point 1.4.1: Nonsteroidal MRA are most appropriate for patients with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.
Practice Point 1.4.2. A nonsteroidal MRA can be added to a RASi and an SGLT2i for treatment of T2D and CKD.
Practice Point 1.4.3. To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.
Practice Point 1.4.4. The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.
Practice Point 1.4.5. A steroidal MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.
GLP-1 receptor agonists
Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).
Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.
Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly.
Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.
Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.
Practice Point 4.2.5. GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist(s); RASi, renin–angiotensin system inhibitor(s); SGLT2i, sodium–glucose cotransporter-2 inhibitor.

lack of confirmatory data on benefits and harms in the real-world clinical environment, and the restriction of high-quality data to one drug in the drug class. These limitations led to a strength of recommendation of Level 2 ("we suggest"), as discussed in detail in the full guideline.

This guideline issues a strong recommendation for use of an SGLT2i in the treatment of people with T2D and CKD, positioning SGLT2i as first-line drug therapy to prevent CKD progression and cardiovascular events, regardless of glycemia (Figures 1–3). This recommendation is based on 11 published clinical trials that provide strong evidence of efficacy and applies to most patients with T2D and CKD for whom an ns-MRA is also suggested. SGLT2i were not standard of care when the FIDELIO-DKD and FIGARO-DKD trials were initiated. However, 877 participants were using an SGLT2i at baseline, and the cardiovascular effects of finerenone, compared with placebo, appeared to be at least as beneficial among people using, versus not using, an SGLT2i.[27] It is also possible that SGLT2i may reduce the risk of hyperkalemia for patients treated concomitantly with an RASi and an ns-MRA.[30,31] These data, combined with complementary mechanisms of action, suggest that the benefits of SGLT2i and finerenone may be additive. Therefore, patients with T2D and CKD who are treated with both an RASi and an SGLT2i and meet criteria for finerenone (including residual albuminuria and non-elevated serum potassium) are appropriate

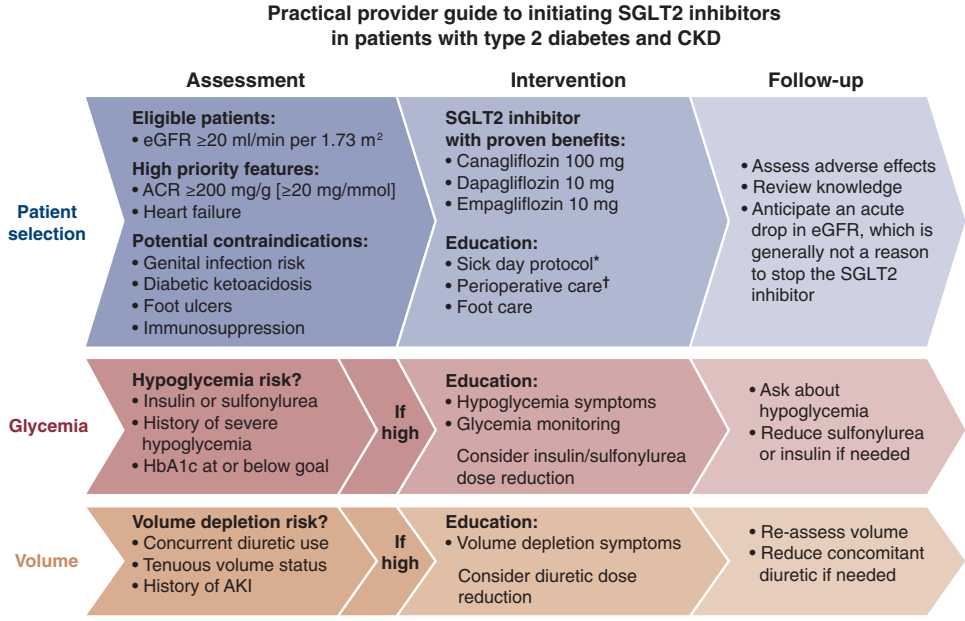

Figure 4 | Practical approach to initiating sodium-glucose co-transporter-2 inhibitors (SGLT2i) in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). *Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold SGLT2i, keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. †Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis; withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required; withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring 1 or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are ≤1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally. ACR, albumin–creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin. Adapted from Zoungas S, de Boer IH. SGLT2 inhibitors in diabetic kidney disease. *Clin J Am Soc Nephrol*. 2021;16:631–633.[19]

candidates for treatment with finerenone. In addition, finerenone may be added to an RASi alone for patients who do not tolerate or are not candidates for an SGLT2i.[25]

To mitigate hyperkalemia risk, the FIDELIO-DKD and FIGARO-DKD trials restricted eligibility to patients with non-elevated serum potassium concentration (after maximizing RASi) and implemented a standardized potassium-monitoring protocol. Clinicians should follow a similar approach to selecting, monitoring, and treating patients with ns-MRA therapy, summarized in Figure 5, to increase the likelihood that the acceptable adverse event profile seen in the FIDELIO-DKD and FIGARO-DKD trials is maintained when applied to clinical practice.

Steroidal MRA, such as spironolactone and eplerenone, have only been rigorously evaluated in long-term clinical outcomes trials in the setting of heart failure. Steroidal MRA are useful for management of heart failure as well as primary hyperaldosteronism and resistant hypertension.[32,33] When a patient is treated with neither a steroidal MRA nor an ns-MRA but has indications for both (e.g., T2D with heart failure and albuminuria on first-line therapies), the most clinically pressing indication should drive selection of the MRA. Currently, an ns-MRA cannot be a replacement for steroidal MRA for the indications of heart failure and hyperaldosteronism. Combining a steroidal MRA and ns-MRA is likely to increase adverse effects and should not be done.

Conclusions

New therapies and high-quality clinical trials have created new opportunities for better treatment of people with diabetes and CKD. This welcome proliferation of options can also cause confusion or controversy that creates a barrier to implementation. One important goal of the updated KDIGO 2022 guideline is to provide a clear, practical, and evidence-based approach to treatment that is useful for a wide variety of patients and healthcare professionals. As always, it is necessary to individualize care for specific patients.

The KDIGO 2022 guideline advocates a layered approach to care, starting with a foundation of lifestyle interventions and first-line pharmacotherapy that has been demonstrated to improve clinical outcomes. Added to this are therapies to reduce the risk of adverse outcomes and control known risk factors for CKD progression and cardiovascular events, such as blood pressure, glycemia, and lipids. Although other guidelines have suggested viewing multifactorial therapy as "pillars" of care,[34–36] the layered approach acknowledges a preference for starting new treatments one at a time and reassessing response and residual risk during refinement of the treatment regimen. In particular, to maximize the chances that combination treatments can be tolerated, it is logical to start medications that affect intrarenal hemodynamics serially (e.g., RASi, SGLT2i, MRA, diuretics, and other antihypertensive medications). In any treatment paradigm, recurrent

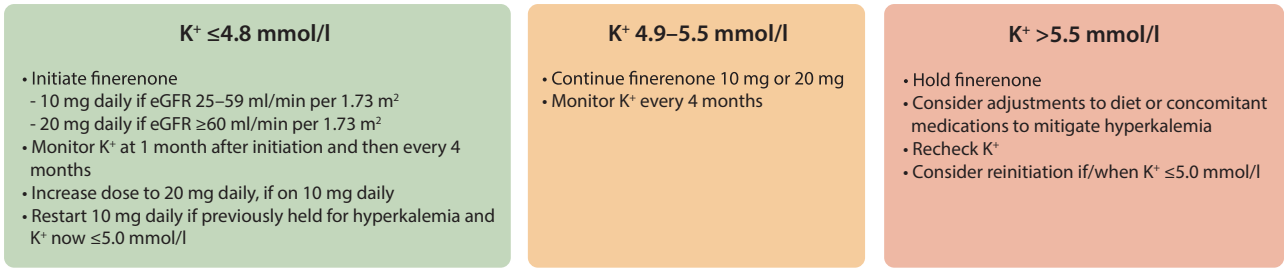

Figure 5 | Serum potassium monitoring during treatment with finerenone. Adapted from the protocols of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD). The United States Food and Drug Administration (FDA) has approved initiation of K^+ <5.0 mmol/l. This figure is guided by trial design and the FDA label and may be different in other countries. Serum creatinine/estimated glomerular filtration rate (eGFR) should be monitored concurrently with serum potassium.

evaluations to address suitability for additional changes are critical to ensure that each patient ultimately receives the optimal full therapeutic regimen.

With new therapies that can reduce progression of CKD and diminish the burden of cardiovascular disease, including heart failure, it is time for those managing diabetes and CKD to focus on preserving kidney function and maintaining well-being rather than on replacing kidney function.[37] The beneficial effects of SGLT2i, ns-MRA, and GLP-1 RA on CKD and cardiovascular disease provide an opportunity to achieve these goals and save millions of lives, but will only benefit people with diabetes and CKD if the use of these drugs is implemented widely and in a timely manner. Successful implementation will necessarily involve collective efforts from all stakeholders, including patients, primary care physicians, specialists such as endocrinologists, cardiologists, and nephrologists, as well as healthcare systems, payors, regulators, and life science industries.[38] It will require concerted action to ensure early detection of CKD with regular screening, education of healthcare professionals regarding multidisciplinary interventions, and empowerment of patients to ensure engagement and self-care.[39] Implementation requires community outreach efforts to make care accessible and equitable, and it is imperative that patient preferences and priorities shape implementation strategies.

The cost of new therapies is a barrier to implementation.[40] Avoiding or delaying costly kidney replacement therapy may make it cost-effective to implement the new therapies,[41–43] but more data are needed to support this possibility. Creating a convincing case for use of CKD therapies as part of a healthcare system strategy for value-based care is essential to translating theoretical cost-effectiveness analyses into reality. This challenge is universal, spanning healthcare globally. This guideline suggests that policymakers and institutional decision-makers implement team-based, integrated care that is focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD.[38]

Multiple professional societies issue recommendations for care of people with diabetes, CKD, or both,[44] and the existence of multiple guidelines can create the appearance of inconsistency. To address this concern, concurrent with development of the 2022 guideline, KDIGO partnered with the ADA, which publishes the influential annual *Standards of Care* for diabetes treatment, to issue a consensus report on the diagnosis and management of diabetes and CKD. The KDIGO-ADA consensus report demonstrates broad consistencies across evidence-based recommendations from the 2 professional societies and emphasizes high-priority interventions.[7] In addition, the consensus report addresses aspects of CKD prevention, screening, and diagnosis, which are important clinical topics not explicitly covered in the KDIGO diabetes and CKD guideline.

Diabetes and CKD continue to be active areas of research, and further advances in diagnosis and treatment are expected. KDIGO will continue to update the diabetes and CKD guideline when major advances occur. At this time, the KDIGO 2022 guideline outlines the state-of-the-art treatment for diabetes and CKD. Implementation of evidence-based treatments is now needed to improve the lives of people living with diabetes and CKD.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Comparison of the 2022 and 2020 KDIGO clinical practice guideline for diabetes management in CKD.

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