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Practical Considerations and Implementation of Sodium-Glucose Co-Transporter-2 Inhibitors in Chronic Kidney Disease: Who, When, and How? A Position Statement by Nephrologists

Anjay Rastogi[1], Ashté Collins[2], Ellie Kelepouris[3], Wayne Kotzker[4], John P. Middleton[5], Minesh Rajpal[6], Prabir Roy-Chaudhury[7], and Glenn M. Chertow[8]

Abstract

Introduction: There remains an unmet need to reduce kidney and cardiovascular risk in patients with chronic kidney disease (CKD). This report is therefore intended to provide real-world clinical guidance to primary care providers on sodium-glucose co-transporter-2 (SGLT2) inhibitor use in patients with CKD, focusing on practical considerations. Initially developed as glucose-lowering drugs, SGLT2 inhibitors preserve kidney function and reduce risks of cardiovascular events and mortality. Clinical benefits of SGLT2 inhibitors in CKD have been demonstrated in multiple clinical trials, yet utilization in practice remains relatively low, likely due to the complexity of labeled indications (past and present) and misconceptions about SGLT2 inhibitors as a class. **Methods:** A panel of 8 US-based nephrologists convened in August 2022 to develop consensus guidance for the primary care community surrounding risk assessment as well as initiation and implementation of SGLT2 inhibitors in patients with CKD. Here, we provide an adapted version of the Kidney Disease: Improving Global Outcomes (KDIGO) heatmap and a treatment-decision algorithm. **Conclusions:** We advocate SGLT2 inhibitors as co-first-line therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors, where RAAS inhibitor dose titration need not be completed before initiation of an SGLT2 inhibitor. In fact, SGLT2 inhibitor therapy may facilitate up-titration or maintenance of optimal RAAS inhibitor dosing. We describe potential strategies to aid implementation of an SGLT2 inhibitor in clinical practice, including improving education and awareness among care providers and patients and dispelling misconceptions about the safety of SGLT2 inhibitors. In summary, we support the use of SGLT2 inhibitors with RAAS inhibitors as co-first-line therapy in most patients with CKD.

Keywords

chronic kidney disease, consensus, KDIGO, SGLT2 inhibitor, treatment algorithm

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Background

Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular events and mortality, as well as diminished functional capacity and health-related quality of life.[1-3] Renin-angiotensin-aldosterone system (RAAS) inhibitors are the cornerstone of therapy for the management of CKD and can preserve kidney function, lowering the risk of progression to kidney failure.[4,5] Nevertheless, the risks of CKD progression and cardiovascular morbidity and mortality remain unacceptably high, presenting an unmet need for additional therapies aimed at sustaining kidney function and preventing or ameliorating complications.

There is substantial evidence from large-scale clinical trials demonstrating that sodium-glucose co-transporter-2 (SGLT2) inhibitors consistently provide kidney and cardiovascular benefits, independent of glucose lowering.[2,6-11] Three pivotal trials of SGLT2 inhibitors in patients with CKD confirmed reductions in progressive kidney disease or cardiovascular death (Table 1); 2 of these 3 trials confirmed benefits among patients with or without type 2 diabetes and micro- or macroalbuminuria, as commonly defined.[2,12-14]

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The primary mechanism underlying the kidney and cardiovascular benefits of SGLT2 inhibitors is thought to involve modulation of tubuloglomerular feedback through decreased sodium resorption and subsequent reduction in intraglomerular pressure through glomerular afferent arteriolar vasoconstriction.[15,16] Notably, the complementary mechanisms of action of SGLT2 inhibitors and RAAS inhibitors provide incremental benefits, particularly if SGLT2 inhibitor use facilitates ongoing use of RAAS inhibitors.[17]

Despite the robust evidence supporting health benefits to be gained from using SGLT2 inhibitors in CKD, prescription patterns suggest only a modest uptake of SGLT2 inhibitors among patients with type 2 diabetes (19% of cases).[18] Similarly, only 5% to 6% of patients with CKD with type 2 diabetes are prescribed SGLT2 inhibitors, with a substantially lower uptake among patients with CKD without type 2 diabetes (approximately 0.3% of cases).[19-21] In addition, a recent analysis based on a US National Prescription Audit showed that endocrinologists were responsible for 11-fold more prescriptions for SGLT2 inhibitors than nephrologists.[22] Clearly, strategies are needed to increase awareness of the evidence supporting use of SGLT2 inhibitors within the nephrology and primary care communities.

This position statement from a panel of nephrologists provides clinical guidance to primary care providers on SGLT2 inhibitor use across a broad spectrum of CKD severity (excluding kidney failure), focusing on the practical considerations—the who, the when, and the how—and challenges to implementation.

Methods

A panel of 8 US-based nephrologists convened for a virtual advisory board on August 30, 2022, with the aim of developing real-world, practical, and easily implemented consensus guidance for primary care providers surrounding the use of SGLT2 inhibitors in patients with CKD. Informed by evidence from randomized, placebo-controlled trials and the most recent KDIGO practice guidelines for CKD (2024) and diabetes management in CKD (2022),[4,5] and combined with extensive experience in real-world clinical settings, this report provides the panel's positions regarding risk assessment, patient identification, and the initiation and implementation of SGLT2 inhibitor therapy.

Consensus Guidance

Overall consensus recommendations from the panel are summarized in Table 2 and Figures 1 and 2.

Risk Assessment: Identifying the Right Patient for SGLT2 Inhibitors

Most patients with CKD, with or without type 2 diabetes and with or without albuminuria, could benefit from SGLT2 inhibitors.[17,23,24] General risk stratification and identification of patients deemed suitable for treatment with SGLT2 inhibitors should be based on the well-established, readily understood, and validated Kidney Disease: Improving Global Outcomes (KDIGO) heatmap.[3,4] However, estimated glomerular filtration rate (eGFR) and albuminuria are only part of the picture, and underlying comorbid conditions and disease state in individual patients should also be considered.[3] Here, the Kidney Failure Risk Equation can provide additional, more individualized risk stratification based on patient-specific factors including age and sex.[25]

A modest adaptation of the KDIGO heatmap is presented here, highlighting points of initiation of SGLT2 inhibitors and monitoring frequency for patients categorized as having an "increased-to-high" risk and "very high" risk of CKD progression (Figure 1), as well as an evidence-based decision algorithm to guide implementation of SGLT2 inhibitors, including referral points from primary to specialist care (Figure 2). Persons screened to assess risk of CKD progression should include those with type 2 diabetes, hypertension, and/or an established or increased risk for atherosclerotic cardiovascular disease,[3] although more recent evidence suggests that a strategy of screening the general population may help reduce the burden of disease and prove cost-effective.[26] Referral from primary to specialist care should be considered, particularly when eGFR is below 45 mL/min/1.73 m^2 or at any eGFR with macroalbuminuria (urinary albumin to creatinine ratio [UACR]

[1]University of California, Los Angeles, CA, USA
[2]George Washington University School of Medicine, Washington, DC, USA
[3]University of Pennsylvania, Philadelphia, PA, USA
[4]Florida Kidney Physicians, Boca Raton, FL, USA
[5]Duke University Medical Center, Durham, NC, USA
[6]Southwest Kidney Institute, Phoenix, AZ, USA
[7]University of North Carolina Kidney Center, Chapel Hill, NC, USA and the WG (Bill) Hefner Salisbury VA Medical Center, Salisbury, NC, USA
[8]Stanford University School of Medicine, Stanford, CA, USA

Corresponding Author:
Glenn M. Chertow, Stanford University School of Medicine, 3180 Porter Drive, A219, Palo Alto, CA 94304, USA.
Email: gchertow@stanford.edu

Table 1. Primary Outcomes in the CKD Trials: CREDENCE, DAPA-CKD, and EMPA-KIDNEY

Eligibility criteria	T2D/no T2D (%)	Primary Outcome	Secondary outcomes	HR primary outcome (95% CI)[a] *P*-value
CREDENCE (canagliflozin[6]; n = 4401)				
eGFR 30-<90 and UACR 300-5000 mg/g, Diagnosis of T2D and HbA1c 6.5%-12.0%	100/0	Composite of ESKD (dialysis ≥30 days, kidney transplantation, or an eGFR <15 for ≥30 days), doubling of sCr for ≥30 days, or death from renal or CV causes	Composite of CV death or hospitalization for HF; composite of CV death, MI, or stroke; hospitalization for HF; composite of ESKD, doubling of sCr, or renal death; CV death; death from any cause; composite of CV death, MI, stroke, or hospitalization for HF or UA	0.70 (0.59-0.82) .00001
DAPA-CKD (dapagliflozin[2]; n = 4304)				
eGFR 25-75 and UACR 200-5000 mg/g	68/32	Composite of sustained decline in eGFR ≥50%, ESKD, or death from renal or CV cause	Composite of sustained decline in eGFR ≥50%, ESKD, or death from renal causes; composite of hospitalization for HF or CV death; death from any cause	0.61 (0.51-0.72) <.001
EMPA-KIDNEY (empagliflozin[13,14]; n = 6609)				
eGFR ≥ 20-<45 (irrespective of UACR) or ≥45-<90 (UACR ≥200 mg/g)	46/54	Composite of sustained decline in eGFR ≥ 40%, sustained eGFR < 10, ESKD (maintenance dialysis or transplant), or death from renal or CV causes	Hospitalization for HF or CV death; all-cause hospitalizations; and death from any cause; components of the primary outcome	0.72 (0.64-0.82) <.001

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, Empagliflozin in Patients with Chronic Kidney Disease; ESKD, end-stage kidney disease; HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; sCr, serum creatinine; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; UA, unstable angina; UACR, urinary albumin to creatinine ratio.
[a]Risk of the primary outcome for SGLT2 inhibitors versus placebo. eGFR reported as mL/min/1.73 m^2.

300 mg/g or higher), although well-informed primary care providers should be ready and able to utilize these agents in practice. Collectively, the heatmap and decision algorithm support the use of SGLT2 inhibitors with RAAS inhibitors as co-first-line therapy in most patients with CKD.

Kidney function should be assessed before initiation of an SGLT2 inhibitor. Since SGLT2 inhibitors as a class lose their glycemic efficacy as kidney function declines, initial labeled indications excluded patients with impaired kidney function—precisely those patients who have the most to gain from the kidney and cardiovascular effects. Approved indications for use are in flux with reports from recently completed clinical trials where, typically, approved indications are restricted to the population(s) enrolled in the trials and thus constitute the evidence base. Nevertheless, in practice, physicians will likely need to rely on clinical judgement whether to initiate or continue treatment with SGLT2 inhibitors in those patients whose eGFR or UACR fall outside the ranges studied in clinical trials. In accordance with clinical guidelines and consensus views,[3,4,27] we concur that SGLT2 inhibitors should be prescribed in patients with early-stage, moderate- to higher-risk disease. We therefore advocate initiation of SGLT2 inhibitors in patients with CKD stages G3a, G3b, and G4, and in patients with albuminuria (UACR ≥30 mg/g) irrespective of eGFR status. This position differs slightly from KDIGO recommendations to initiate SGLT2 inhibitors among patients with UACR ≥200 mg/g,[4] the rationale being that, in current practice, screening with UACR is completed in only a minority of individual with type 2 diabetes (despite clinical practice guideline-based recommendations), and very rarely among those without type 2 diabetes.[28] Moreover, retrospective analysis of clinical trials of dapagliflozin across a broad range of patients with CKD showed dapagliflozin initiation was associated with a clinically meaningful attenuation of decline in kidney function compared with non-initiation, and that dapagliflozin effectiveness may extend to patients with CKD and UACR <200 mg/g.[29] Type 2 diabetes should not be considered a prerequisite for initiation of SGLT2 inhibitors.[23,24,30] The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)[2] and Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY)[13] trials demonstrated that SGLT2 inhibitors resulted in kidney and

Table 2. Consensus Guidance from a Panel of 8 US-Based Nephrologists.

Topic	Consensus guidance
Risk assessment: identifying the right patient for SGLT2 inhibitors	• Most patients with CKD could benefit from initiation of an SGLT2 inhibitor • General risk stratification and identification of patients suitable for initiation of an SGLT2 inhibitor should be based on the KDIGO heatmap, in conjunction with the KFRE for more individualized risk stratification • Patient referral from primary to specialist care should be considered when eGFR is below 45 mL/min/1.73 m^2, or at any eGFR with macroalbuminuria • Individuals who should be screened to assess risk of CKD progression include those with type 2 diabetes, hypertension, or established ASCVD or those at elevated risk for ASCVD • Early initiation of SGLT2 inhibitor should be considered, including by primary care physicians, before referral to a nephrologist • Risk stratification will likely be based on eGFR rather than UACR due to real-world suboptimal UACR monitoring • An SGLT2 inhibitor can be initiated in patients with CKD without albuminuria and/or type 2 diabetes
Initiation of SGLT2 inhibitors in patients with CKD	• SGLT2 inhibitors should be considered as co-first-line therapy alongside RAAS inhibitors in patients with CKD at risk of progression • If feasible, the interval between initiation of a RAAS inhibitor and an SGLT2 inhibitor should ideally be within 3 months; CV effects of SGLT2 inhibitors are evident as early as several weeks following initiation • Maximization and/or optimization of RAAS inhibitor dosing should not prevent or delay initiation of SGLT2 inhibitor therapy • Initiation of SGLT2 inhibitors must align with local prescribing information and consider follow-up needs ○ Prior to initiation of an SGLT2 inhibitor, patients should not be volume depleted, and physical examination should be performed including assessment of blood pressure and laboratory safety measures (hematocrit and electrolytes) ○ Periodic monitoring of a patient's kidney and CV risk profile is recommended for patients treated concomitantly with RAAS inhibitors and SGLT2 inhibitors, but routine assessment of kidney function is not required following initiation of an SGLT2 inhibitor if patients are already on a maximally tolerated RAAS inhibitor dose • Following SGLT2 inhibitor initiation, treatment can continue if eGFR falls below initiation thresholds, and following initiation of dialysis for CV benefits or potential preservation of residual kidney function • Treatment with an SGLT2 inhibitor should be discontinued in clinical situations predisposing to ketoacidosis (temporary discontinuation), and if signs and symptoms of ketoacidosis occur
Implementation of SGLT2 inhibitors in patients with CKD	• Primary care providers should actively prescribe SGLT2 inhibitors in patients with CKD; ideally being able to prescribe SGLT2 inhibitors before referral to specialist care; and with support/guidance from nephrologists, as required • Enhanced education and awareness surrounding SGLT2 inhibitors among primary care professionals and patients is needed to help dispel common misconceptions about this class of drugs • All patients with CKD should receive counseling about sick day medication management and when to stop/resume their SGLT2 inhibitor

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KFRE, Kidney Failure Risk Equations; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose co-transporter-2; UACR, urinary albumin to creatinine ratio.

cardiovascular benefits evident in participants without type 2 diabetes, and independent of glucose lowering in participants with type 2 diabetes.

Initiation of SGLT2 Inhibitors in Patients With CKD

To delay CKD progression, SGLT2 inhibitors should be considered (along with RAAS inhibitors) as co-first-line therapy in patients with CKD.[31] SGLT2 inhibitors can be initiated at the standard recommended dose with respect to beneficial effects on kidney and cardiovascular outcomes[32] (higher doses of SGLT2 inhibitors are sometimes selected for incremental glucose-lowering effects in patients with normal or near-normal kidney function). Initiation of a RAAS inhibitor and an SGLT2 inhibitor should occur over an approximate 3-month period, recognizing that the beneficial cardiovascular effects of SGLT2 inhibitors can be

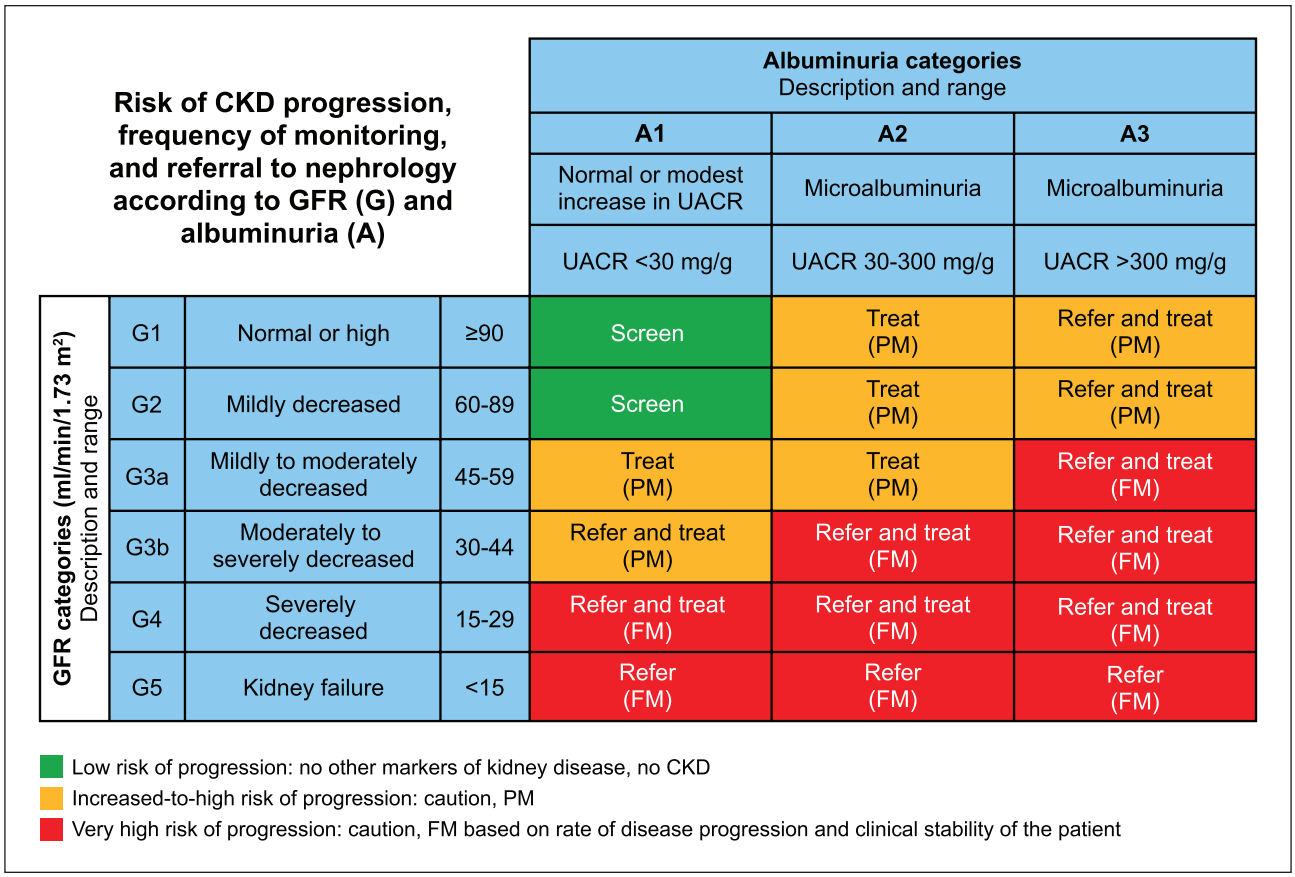

Figure 1. Modified KDIGO risk prediction heatmap. Risk of CKD progression, frequency of visits, and referral to nephrology specialists according to GFR and albuminuria.
Source: Adapted with permission from de Boer et al.[3]
Abbreviations: CKD, chronic kidney disease; FM, frequent monitoring; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PM, periodic monitoring; SGLT2, sodium-glucose co-transporter-2.
Bracketed acronyms are intended to provide a broad guide to the frequency of screening or monitoring. Treat refers to co-initiation of a SGLT2 inhibitor.

seen as early as several weeks following treatment initiation,[2] and accounting for challenges in accessing primary and specialty care in the modern era. Members of the panel were unanimous in recommending that up-titration/optimization of RAAS dosing should not prevent or delay initiation of SGLT2 inhibitor therapy. Initiation of SGLT2 inhibitors before up-titration/optimization of RAAS inhibitors could facilitate the latter, since co-administration of SGLT2 inhibitors can reduce the likelihood of RAAS inhibitor-induced hyperkalemia,[33,34] a frequent reason for discontinuation or under-dosing of RAAS inhibitor therapy. Gradual up-titration of RAAS inhibitors could also prevent or ameliorate other complications, including relative hypotension and acute decrements in kidney function associated with other therapies for hypertension that provide less potent or no apparent kidney or cardiovascular benefit.

The panel also suggested that up-titration of a RAAS inhibitor and initiation of a mineralocorticoid receptor antagonist (eg, finerenone) should be staggered (Figure 2) similarly to SGLT2 inhibitors, as these agents promote an initial hemodynamic reduction in GFR.[35] Here, the interval should factor in the potential for a drop in GFR, and allow time for monitoring of blood pressure, serum creatinine, and serum potassium. While periodic monitoring of a patient's kidney and cardiovascular risk profile is recommended for patients treated concomitantly with RAAS inhibitors and SGLT2 inhibitors, routine assessment of kidney function is not required following initiation of an SGLT2 inhibitor if patients are already on a maximally tolerated dose of a RAAS inhibitor.[3,31] Use of the RAAS inhibitor/SGLT2 inhibitor combination can be continued following initiation of dialysis for cardiovascular benefits or potential preservation of residual kidney function. SGLT2 inhibitors should, however, be temporarily discontinued in clinical situations known to predispose to ketoacidosis (eg, prolonged fasting due to acute illness or

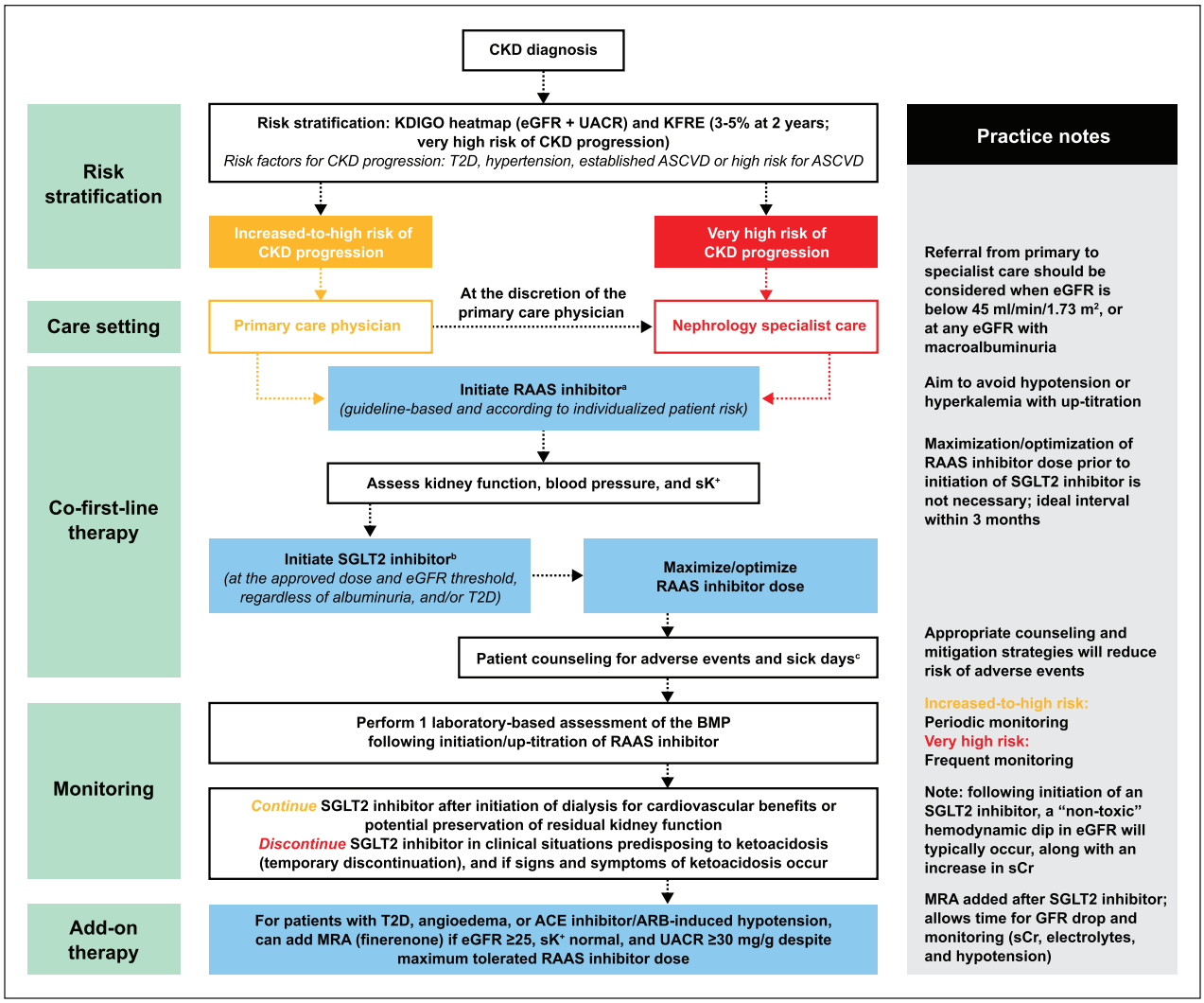

Figure 2. Decision algorithm supporting initiation of SGLT2 inhibitors.
Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMP, basic metabolic profile; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; KFRE, Kidney Failure Risk Equations; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; sCr, serum creatinine; SGLT2, sodium-glucose co-transporter-2; sK^+, serum potassium; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.
[a]RAAS inhibitor refers to ACE inhibitor or angiotensin receptor blocker.
[b]No contraindications as per the label and pending no safety concerns. The lower limit of eGFR is dependent on the specific SGLT2 inhibitor used; continue until ESKD.[3]
[c]Patients should be provided with sick day advice, whereby they are advised to hold their SGLT2 inhibitor until resolution of symptoms. Some patients, including those with heart failure, may require liberalization of fluid intake if they are euvolemic when initiating an SGLT2 inhibitor.

post-surgery) and discontinued if signs and symptoms of ketoacidosis occur. The risk of hypovolemia with SGLT2 inhibitors is low. Similarly, hypoglycemia risk is low with SGLT2 inhibitors, although a lower dose of insulin or insulin secretagogue might be used to minimize risk.

Implementation

In clinical practice, patient access to resources can be restricted for a variety of reasons, thus constraining the opportunity for physicians to consider the individual risk of CKD progression and the potential for complications and implement the ideal monitoring program. Nevertheless, SGLT2 inhibitors represent an efficacious and well-tolerated strategy as co-first-line therapy to slow CKD progression and reduce complications in patients with CKD. More extensive education and awareness will likely increase prescribing of SGLT2 inhibitors by non-endocrinologist primary care providers (including internal medicine and family medicine physicians, as well as advanced practice providers

working in nephrology or primary care) to patients who do not require referral to specialist care.[31]

As is the case with RAAS inhibitors, it is important to remind primary care providers that the increase in serum creatinine observed after initiation of an SGLT2 inhibitor is related to the drug's mechanism of action, and that patients who experience an acute decline in eGFR when beginning treatment with SGLT2 inhibitors do not experience higher rates of CKD progression.[36] Moreover, SGLT2 inhibitor use appears to protect patients from acute kidney injury.[17] Evidence from clinical trials should be used to support SGLT2 inhibitors as safe and well tolerated in patients with CKD, with no evident increase in risk of acute kidney injury, clinical manifestations of volume depletion, Fournier's gangrene, amputation, or other complications of peripheral arterial disease, hypoglycemia, or hypotension.[2,12,13,31,32,37] There is a low risk of euglycemic diabetic ketoacidosis in some settings (patients who are fasting and/or have acute illness) that can be mitigated by temporarily withholding treatment. Indeed, some have advocated putting SGLT2 inhibitors "on hold" for "sick day management" in the setting of acute illness or in anticipation of radiographic or surgical procedures.[38]

Primary care providers must play a role in keeping patients informed as to the effects of SGLT2 inhibitors, including patients with type 2 diabetes and multiple risk factors, as well as those with established heart failure and CKD.[17,31] CKD management is based on a collaborative, team-based care model such that primary care providers should actively prescribe SGLT2 inhibitors in patients with CKD, reserving nephrology consultations for patients with more rapid progression of disease or other complications that might obligate additional therapy. Strategies to increase patient understanding of SGLT2 inhibitors should be complemented by comprehensive patient counseling surrounding sick day medication management,[39] including whom to contact, when to stop/hold SGLT2 inhibitor until resolution of symptoms/illness, potential adverse events, the monitoring of blood glucose and ketone levels and, in patients with type 2 diabetes, early recognition of the signs and symptoms of diabetic ketoacidosis.[32,40]

Given the clear clinical benefits of SGLT2 inhibitors in CKD, further considerations must be given regarding additional expenditures on disease management against long-term clinical benefits achieved through reduced downstream disease and health care burden and improved patient health-related quality of life. Several analyses have assessed the cost-effectiveness of SGLT2 inhibitors to inform decision-making.[41,42] For example, use of dapagliflozin increased medication costs but overall was cost-effective, by currently accepted criteria and across several countries, for the management of patients across a broad spectrum of CKD severity, with or without type 2 diabetes. Although short-term costs associated with SGLT2 inhibitors increase, delayed CKD progression to kidney failure and kidney replacement therapy and reduced incidence of hospitalization for heart failure provide important cost offsets.

Conclusions

The risk of CKD progression and cardiovascular events despite the provision of RAAS inhibitors represents a significant unmet medical need that requires prompt and effective action by primary care professionals involved in the care of patients with kidney disease. This panel of nephrologists supports the contention that SGLT2 inhibitors should be considered as a co-first-line therapy with RAAS inhibitors as part of integrated and individualized CKD care strategies. Adopting this approach will optimize the benefits afforded by SGLT2 inhibitors and RAAS inhibitors and help to further reduce disease burden; this approach will potentially be refined further through emerging real-world evidence. Earlier recognition of kidney disease and the prescription of SGLT2 inhibitors to patients at risk for CKD progression and cardiovascular events by nephrologists and primary care providers should lead to health benefits for the many patients with CKD and should ultimately reduce the burden of kidney failure in the population. Our consensus positions regarding risk assessment, initiation, and implementation of SGLT2 inhibitors, based on published evidence and extensive clinical experience, may help the primary care community to integrate SGLT2 inhibitors into clinical care to optimize the management of patients with CKD.

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Author Contributions

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ORCID iDs

Anjay Rastogi https://orcid.org/0000-0002-8117-6010
Glenn M. Chertow https://orcid.org/0000-0002-7599-0534

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