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EXPERT OPINION

Impact of Sodium-Glucose Cotransporter-2 Inhibitors in the Management of Chronic Kidney Disease: A Middle East and Africa Perspective

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Abstract: Chronic kidney disease (CKD) is a major public health concern in the Middle East and Africa (MEA) region and a leading cause of death in patients with type 2 diabetes mellitus (T2DM) and hypertension. Early initiation of sodium-glucose cotransporter - 2 inhibitors (SGLT-2i) and proper sequencing with renin-angiotensin-aldosterone system inhibitors (RAASi) in these patients may result in better clinical outcomes due to their cardioprotective properties and complementary mechanisms of action. In this review, we present guideline-based consensus recommendations by experts from the MEA region, as practical algorithms for screening, early detection, nephrology referral, and treatment pathways for CKD management in patients with hypertension and diabetes mellitus. This study will help physicians take timely and appropriate actions to provide better care to patients with CKD or those at high risk of CKD.

Keywords: chronic kidney disease, nephrology referral, screening, sodium-glucose cotransporter-2 inhibitors

Introduction

Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide.[1] The global prevalence of CKD is predicted to be 13.4% (11.7% to 15.1%), with 4.9–7.1 million individuals requiring kidney replacement therapy.[2] In the majority of the Middle East, diabetes mellitus (DM) and hypertension account for 45%–74% of end-stage kidney disease (ESKD).[3,4]

Controlling hyperglycemia,[5] hypertension,[5] hyperlipidemia,[6] and obesity[7,8] along with lifestyle modification[9] and the use of cardiorenal protective medications[10] are the mainstays of treatment for slowing CKD progression. A post-hoc analysis of the Nephropathy in Diabetes type-2 (NID-2) trial showed that multifactorial intensive treatment (a pre-specified algorithm for managing hypertension, hyperglycemia, and dyslipidemia) resulted in an increased number of well-managed risk factors compared to standard of care that gradually improved the cardiovascular prognosis in patients with type 2 diabetes mellitus (T2DM) and albuminuria.[11] Mima et al, suggested that enhancing the endogenous protective factors, such as insulin, glucagon-like peptide-1, and others may neutralize the adverse effects of hyperglycemia and prevent diabetic nephropathy.[12] Enriching of these endogenous factors involves life style modifications, the reduction in oxidative stress, and application of targeted therapies that can modulate the activity of protein kinase C-β and nuclear factor κB.[12,13] Among the available therapeutic arsenals, the cardioprotective effects of sodium-glucose cotransporter - 2 inhibitors (SGLT-2i) in patients

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with T2DM are now well proven.[14,15] The results of relative risk reduction of kidney and heart failure (HF) outcomes have been demonstrated in patients with HF/CKD with and without T2DM.[16–20] Recent breakthroughs in therapeutic and preventive approaches for CKD management,[21] training and advocacy for this cause, and inclusion of CKD in national non-communicable disease policies are strategies that could be implemented to improve the management of CKD in low- and middle-income countries.[3,22]

Methodology

A panel of 12 key external experts (KEEs) from the Middle East and Africa (MEA) region (Egypt [n=2], Iraq [n=1], Jordan [n=1], Kingdom of Saudi Arabia [n=1], Kuwait [n=1], Lebanon [n=1], Morocco [n=1], Turkey [n=2], and United Arab Emirates [n=2]) congregated and discussed the current unmet need for the management of CKD, along with the use of SGLT-2i in CKD management in the MEA region. This manuscript is an outcome of a literature review, KEE group discussion, and consensus recommendations to provide an action plan for the screening, early detection, and management of CKD in the MEA region.

Screening and Early Diagnosis of CKD in MEA

Up to 90% of individuals with CKD stage 3 are undiagnosed in primary care settings; the majority are diagnosed at the advanced stage of the disease with the availability of limited treatment options for either dialysis or organ transplantation.[23] Early screening, diagnosis, and management of patients with CKD by primary care physicians (PCPs) are crucial owing to the associated poor clinical outcomes (ESKD, cardiovascular disease, and increased mortality) with progressive CKD.[24,25] Hypertension is another risk factor that is undertreated in most Middle Eastern countries such as Morocco; only 17.1% of the patients had controlled hypertension with a history of hypertension and received antihypertensive medications and/or lifestyle and dietary advice.[26] Furthermore, the use of a single threshold of estimated glomerular filtration rate (eGFR; < 60 mL/min/1.73 m^2) in classifying CKD stages 3 to 5 may lead to underdiagnoses of CKD in young adults with eGFR > 60 mL/min/1.73 m^2 with or without proteinuria or other markers of kidney damage.[27]

Several studies have shown the cost-effectiveness of population screening for CKD, considering the incidence of ESKD.[28–30] The American Diabetes Association released its 2023 Standards of Medical Care in Diabetes, which suggested that eGFR should be measured twice a year to guide their treatment in patients with DM with a urine albumin-creatinine ratio (UACR) of ≥300 mg/g and/or an eGFR of 30 to 60 mL/min/1.73 m^2.[31] Table 1 presents the summary of international guidelines for CKD management.[31–35] In view of this, our panel suggested recommendations for screening, diagnosis, and a nephrology referral pathway to provide a better and more standardized service to the patients (Figures 1 and 2).

Implementation of an early screening program and appropriate treatment by specialists can delay CKD progression, prevent ESKD, and improve patient outcomes. One such initiative is the "SEARCH" program for Screening Early Renal Complications in High-risk patients. This program is an ongoing project implemented in Europe and other emerging countries. The goal of the SEARCH program is to identify awareness among PCPs about early CKD consequences in high-risk patients (DM or hypertension).[36] The involvement of PCPs or general practitioners is crucial for its success. However, PCPs need expert guidance to initiate screening. Population screening, data mining, and disease awareness campaigns are three fundamental strategies for early CKD screening. Al-Ghamdi et al, suggested that national renal associations, nephrology conferences, and memorial days such as World Kidney Day can be used to raise awareness at patients and PCPs levels about novel therapies and the importance of early detection and management of CKD.[37]

Evidence Supporting the Use of SGLT-2i for Management of Population at High-Risk of CKD

Several real-world studies and randomized controlled trials have shown the renoprotective effect of SGLT-2i.[16,38,39] The Japan Chronic Kidney Disease Database registry demonstrated a renoprotective effect of SGLT-2i, with no evidence of a decline in the rate of kidney function decline or the presence of proteinuria.[39] Table 2 presents an overview of major randomized controlled trials for SGLT-2i.[10,14,19,40–44] Canagliflozin, dapagliflozin, and empagliflozin have shown frequent regression of albuminuria and reduced risk of kidney-specific outcomes and death from kidney-related causes.[14,40–42] The DAPA-CKD trial

Table 1 Summary of Recommendations from International Guidelines for Screening, Diagnosis and Referral of Patients with CKD

Guidelines	Screening Population	Screening/Diagnosis	Referral to Nephrologist
KDIGO[28,29]	• Patients with hypertension, diabetes, and CVD • Screening program for early detection in high-risk population based on demographics, comorbidities, environmental exposures, or genetic risk factors	Estimate eGFR and ACR • Once per year ○ G1 (if CKD present*) with A1 or A2 ○ G2 (if CKD present*) with A1 or A2 ○ G3a with A1 • Twice per year ○ G1 or G2 with A3 ○ G3a with A2 ○ G3b with A1 • Thrice per year ○ G3a with A3 ○ G3b with A2 or A3 ○ G4 with A1 or A2 • ≥4 times per year ○ G4 with A3 ○ G5 with A1, A2, or A3	• AKI or abrupt sustained fall in eGFR • eGFR <30 mL/min/1.73 m^2 (eGFR categories G4 to G5)** • Consistent finding of significant albuminuria (UACR of ≥300 mg/g or UAER of ≥300 mg/24 hours) • Progression of CKD • Urinary red cell casts, RBC >20 per high power field sustained and not readily explained • CKD and hypertension refractory to treatment with 4 or more antihypertensive agents • Persistent abnormalities of serum potassium • Recurrent or extensive nephrolithiasis • Hereditary kidney disease
ADA[26]	Patients with • T1DM or T2DM with existing CVD • hypertension	Estimate eGFR and spot UACR at least yearly once • patients with T1DM with disease duration of ≥5 years • all patients with T2DM regardless of treatment	• eGFR <30 mL/min/1.73 m^2 • Active urinary sediment (containing red or white blood cells or cellular casts) • Rapidly increasing albuminuria or nephrotic syndrome • Rapidly decreasing eGFR • Absence of retinopathy (in T1DM) • Uncertainty about the etiology of kidney disease • For difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure control, metabolic bone disease, resistant hypertension, or electrolyte disturbances)

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Table 1 (Continued).

Guidelines	Screening Population	Screening/Diagnosis	Referral to Nephrologist
Kidney Health Australia[27]	Patients with • diabetes • hypertension • existing CVD • family history of kidney failure • obesity (BMI ≥30kg/m^2) • smoking • age over 60 in the absence of other risk factors • aboriginal or Torres Strait Islander origin aged ≥30 years • history of acute kidney injury	Estimate eGFR and spot UACR every 1 to 2 years in individuals at high-risk of CKD	• Reduction in GFR is more than 25% below the baseline value • A sustained decrease in eGFR of 25% or more within 12 months • A sustained decrease in eGFR of 15 mL/min/1.73m^2 per year • Stage 4 or 5 CKD of any cause • UACR ≥ 300 mg/g • CKD with uncontrolled hypertension despite at least three antihypertensive agents
KDOQI[30]	Patients with • diabetes • hypertension • autoimmune diseases • systemic infections • urinary tract infections • urinary stones • lower urinary tract obstruction • neoplasia • family history of CKD • recovery from acute kidney failure • reduction in kidney mass • exposure to certain drugs • low birth weight • older age • exposure to certain chemical and environmental conditions • low income/education • US ethnic minority status: African American, American Indian, Hispanic, Asian, or Pacific Islander	Estimate eGFR and ACR • Once per year ○ G1 (if CKD present*) with A1 or A2 ○ G2 (if CKD present*) with A1 or A2 ○ G3a with A1 • Twice per year ○ G1 or G2 with A3 ○ G3a with A2 ○ G3b with A1 • Thrice per year ○ G3a with A3 ○ G3b with A2 or A3 ○ G4 with A1 or A2 • > 4 times per year ○ G4 with A3 ○ G5 with A1, A2, or A3	• Acute kidney injury • eGFR of <30 mL/min/1.73 m^2 • Rapid decline in eGFR • Albuminuria level of ≥300 mg/g • CKD progression, or CKD • Hypertension refractory to treatment with ≥4 antihypertensive agents • Urinary red cell casts • RBC >20 per high power field sustained and not readily explained • Persistent abnormalities of serum potassium • Recurrent or extensive nephrolithiasis • Hereditary kidney disease

Notes: GFR categories: G1, eGFR of ≥90 mL/min/1.73 m^2; G2, eGFR of 60 to 89 mL/min/1.73 m$^{2;}$ G3a, eGFR of 45 to 59 mL/min/1.73 m^2; G3b, eGFR of 30 to 44 mL/min/1.73 m^2; G4, eGFR of 15 to 29 mL/min/1.73 m^2; G5, <15 mL/min/1.73 m^2. Albuminuria categories: A1, UACR of <30 mg/g; A2, UACR of 30 to 300 mg/g; A3, UACR of >300 mg/g. *In case kidney structural abnormalities. **If this is a stable isolated finding, formal referral might not be required.
Abbreviations: ADA, American Diabetes Association; ACR, albumin-creatinine ratio; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; RBC, red blood cell; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio; UAER, urine albumin excretion rate; US, United States.

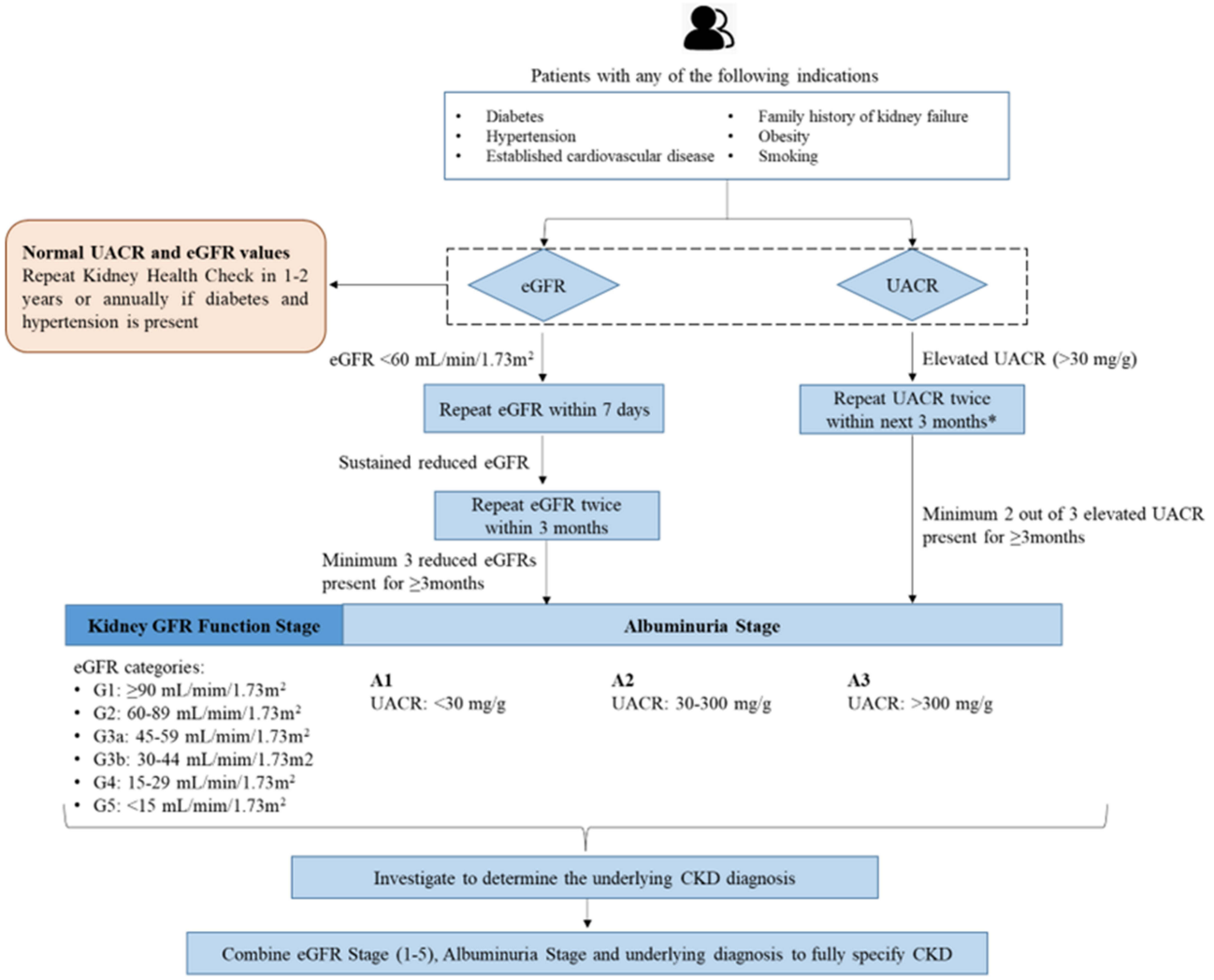

Figure 1 Recommended algorithm for screening and diagnosis of CKD.
Note: *Prefer first morning void.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio.

showed that the dapagliflozin group had a significantly lower occurrence of a composite of a sustained decline in the eGFR of at least 50%, ESKD, or death from kidney or cardiovascular causes (9.2% vs 14.5%; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.51, 0.72; p<0.001) compared to placebo.[16] Results of the CVD-REAL 3 (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study demonstrated that initiation of SGLT-2i was associated with a slower decline in eGFR rate compared to other antidiabetic drugs.[38] Another large registry-based cohort study using nationwide data from routine clinical practice in Sweden, Denmark, and Norway showed that SGLT-2i lowered the risk of kidney events compared with dipeptidyl peptidase 4 inhibitor.[45]

Practical Considerations for the Usage of SGLT-2i in CKD Management

Although initiation of SGLT-2i may initially decrease the glomerular filtration rate (GFR) and increase serum creatinine level, these changes are usually short-lived and may occur even with improvement in patient outcomes, and long-term use of SGLT-2i may slow the process of worsening kidney function.[10,19] SGLT-2i can provide renal protection by improving mitochondrial dynamics and reducing oxidative stress and metabolic burden in proximal tubular renal cells. SGLT-2i also decrease albuminuria, delay the progression of nephropathy, and defer the initiation of renal replacement therapy.[46–49] A post hoc analysis from the CREDENCE trial revealed that in patients with T2DM and CKD for each 30%

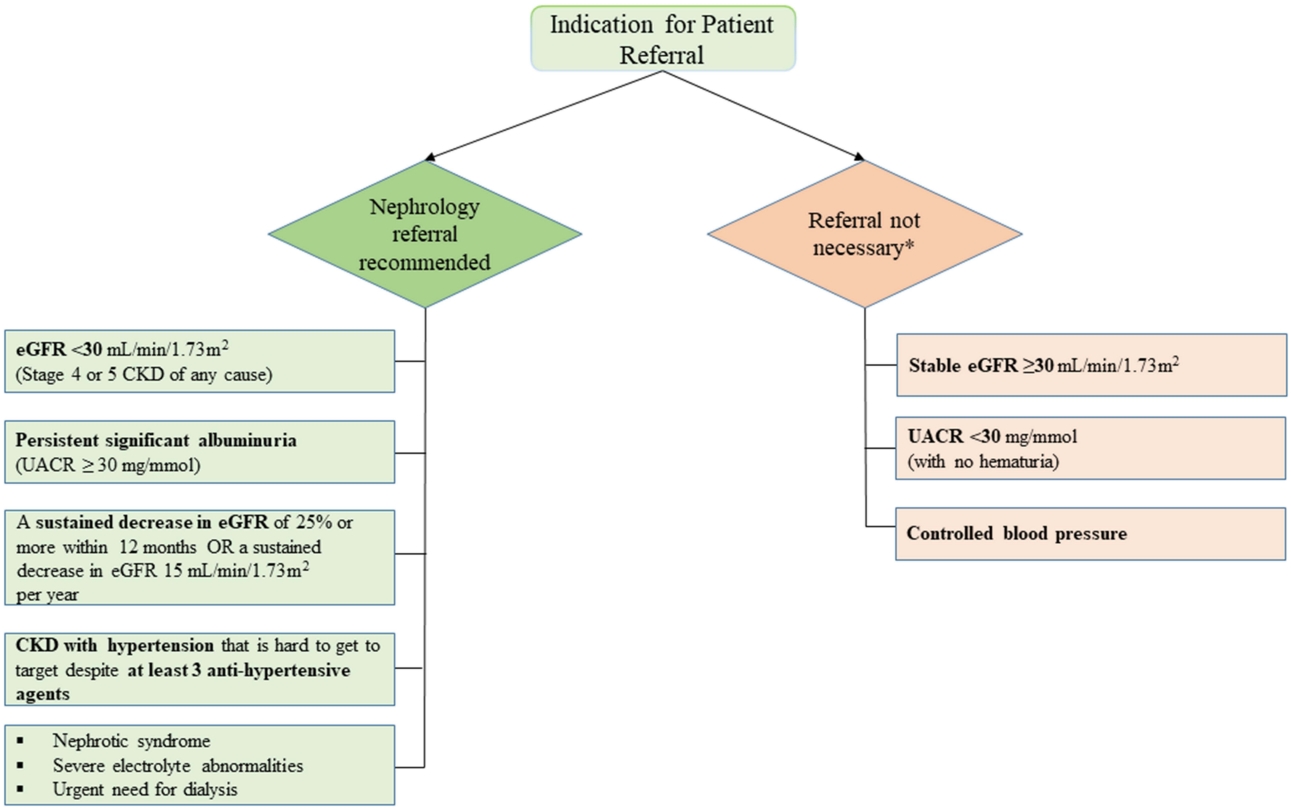

Figure 2 Recommended nephrology referral pathway.
Note: *In the absence of other referral indicators.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio.

decrease in urinary albumin-creatinine ratio during the initial 26 weeks of treatment, SGLT-2i (canagliflozin) use was associated with a 29% (HR, 0.71; 95% CI, 0.67, 0.76) reduced risk of kidney outcomes compared to placebo.[50] Although canagliflozin resulted in early and sustained reductions in albuminuria, residual albuminuria was noted that was associated with kidney and cardiovascular events. These findings highlight the importance of monitoring albuminuria during canagliflozin treatment to effectively address both renal and cardiovascular prognoses.[50]

According to the European Society of Cardiology (ESC) guidelines, SGLT-2i, renin-angiotensin-aldosterone system inhibitor (RAASi), or angiotensin receptor-neprilysin inhibitors should not be promptly interrupted due to a transient decrease in renal function. An increase in serum creatinine of <50% above baseline, as long as it is <266 µmol/L (3 mg/dL), or a decrease in eGFR of <10% from baseline, provided eGFR is >25 mL/min/1.73 m^2 can be considered as acceptable.[51] Furthermore, there are few adverse events reported with dapagliflozin in patients with and without T2DM.[15,52] Despite being a rare adverse event, diabetic ketoacidosis is more common in patients with T2DM in the dapagliflozin arm compared with the placebo arm (0.3% versus 0.1%; p=0.02).[15] Results from the DAPA-CKD trial showed that SGLT-2i (dapagliflozin) safely reduced kidney and cardiovascular events independent of baseline diabetes and glycemic status. Dapagliflozin and placebo arms have similar overall incidence of adverse events and serious adverse events in patients with normoglycemia or prediabetes.[16,53] In addition, no events of diabetic ketoacidosis and severe hypoglycemia were observed in patients without T2DM.[16] There were fewer occurrences of hyperkalemia and kidney-related adverse events were observed.[53,54]

Complementary Mechanism of Action of SGLT-2i and RAASi

Despite the availability of RAASi, there is a considerable risk of CKD progression with current therapeutic agents due to underdiagnosis, treatment with kidney-protective agents (SGLT-2i), or lower effectiveness of RAASi compared to the combined use of RAASi and SGLT-2i to slowing CKD progression.[55–57] A United States-based retrospective

Table 2 Clinical Trials Describing the Kidney-Protective Outcome of SGLT-2i

Name of Study	Design	Objective	Population Characteristics	Number of Patients	Treatment Modality	Outcome
CANVAS and CANVAS-R[9]	Randomized, placebo-controlled study	Effect of canagliflozin on CV, kidney, and safety outcomes	Patients with • T2DM • established ASCVD-65.6%	10,142 (CANVAS:4330, CANVAS-R:5812)	CANVAS (1:1:1) – canagliflozin (300 mg), canagliflozin (100 mg), or matching placebo CANVAS-R (1:1) – canagliflozin: 100 mg with an optional increase to 300 mg or matched placebo	• Canagliflozin group (versus placebo) had ○ less frequent progression of albuminuria (89.4 versus 128.7 participants with an event per 1000 patient-years) with HR of 0.73 (95% CI, 0.67 to 0.79) ○ more frequent regression of albuminuria (293.4 versus 187.5 participants with regression per 1000 patient-years; HR, 1.70; 95% CI, 1.51 to 1.91) ○ a composite outcome of sustained 40% reduction in eGFR, the need for kidney replacement therapy, or death from kidney causes (HR, 0.60; 95% CI, 0.47 to 0.77) • A greater effect was observed in in CANVAS-R (HR, 0.64; 95% CI, 0.57 to 0.73) compared to CANVAS (HR, 0.80; 95% CI, 0.72 to 0.90; p=0.02 for homogeneity)
CREDENCE[37]	Randomized, double-blind, event-driven, placebo-controlled, multicenter study	Effects of canagliflozin on kidney and CV outcomes in participants with diabetic nephropathy	Patients with • T2DM • diabetic nephropathy	4401	Canagliflozin 100 mg versus placebo	• Canagliflozin group (versus placebo) had 30% lower relative risk of composite of ESKD (dialysis, transplantation, or a sustained eGFR of <15 mL/minute/1.73 m^2), a doubling of the serum creatinine level, or death from kidney or CV causes with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR, 0.70; 95% CI, 0.59 to 0.82; p=0.00001) • Canagliflozin group (versus placebo) had lower ○ relative risk of the kidney-specific composite of ESKD, a doubling of the creatinine level, or death from kidney causes by 34% (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001) ○ relative risk of ESKD by 32% (HR, 0.68; 95% CI, 0.54 to 0.86; p=0.02) • Risk of CV death, MI, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; p=0.01 and HHF (HR, 0.61; 95% CI, 0.47 to 0.80; p<0.001)

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Table 2 (Continued).

Name of Study	Design	Objective	Population Characteristics	Number of Patients	Treatment Modality	Outcome
DAPA-CKD[11]	International, multicenter, randomized, double-blind, parallel group, placebo-controlled study	Effect of dapagliflozin on kidney outcomes and CV mortality in patients with CKD	Patients with • CKD • with or without T2DM	4304	Dapagliflozin 10 mg versus placebo	• Dapagliflozin group (versus placebo) had lower ○ occurrence of composite of a sustained decline in the eGFR of at least 50%, ESKD, or death from kidney-related or CV (9.2% versus 14.5%; HR, 0.61; 95% CI, 0.51 to 0.72; p<0.001; number needed to treat to prevent one primary outcome event, 19; 95% CI, 15 to 27) ○ occurrence of death (4.7% versus 6.8%; HR, 0.69; 95% CI, 0.53 to 0.88; p=0.004) ○ risk of composite of a sustained decline in the eGFR of at least 50%, ESKD, or death from kidney-related causes (HR, 0.56; 95% CI, 0.45 to 0.68, p<0.001) ○ risk for the composite of death from CV causes or HHF (HR, 0.71; 95% CI, 0.55 to 0.92; p=0.009)
DECLARE-TIMI 58[34,35]	Randomized, double-blind, multinational, placebo-controlled study	Effect of dapagliflozin on CV outcomes	Patients with established ASCVD-40.6%	17,160	Dapagliflozin 10 mg versus matched placebo (1:1)	DECLARE-TIMI 58, 2019 • Dapagliflozin group (versus placebo) had ○ reduced risk of kidney-specific outcome (HR, 0.53; 95% CI, 0.43 to 0.66; p<0.0001) ○ reduced risk of cardiorenal secondary composite outcome (HR, 0.76: 95% CI, 0.67 to 0.87; p<0.0001) ○ reduced risk of ESKD or kidney death (HR, 0.41; 95% CI, 0.20–0.82; p=0·012) ○ 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min/ 1·73 m^2 (HR, 0.54; 95% CI, 0.43 to 0.67; p<0.0001) DECLARE-TIMI 58, 2021 • Dapagliflozin group (versus placebo) had ○ reduced risk of kidney-specific outcome (HR, 0.51; 95% CI, 0.37 to 0.69) and CV death or HHF (HR, 0.84; 95% CI, 0.67 to 1.04) ○ higher eGFR (p<0.001) ○ lowered HbA_{1C}, SBP, and urinary albumin-to-creatinine ratio (p<0.001)

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EMPA-REG[38]	Randomized, double-blind, placebo-controlled study	Long-term kidney effects of empagliflozin	Patients with • T2DM • eGFR of at least 30 mL/minute per 1.73 m^2	4124	Empagliflozin 10 mg or 25 mg versus placebo	• Empagliflozin group (versus placebo) had significant ○ relative risk reduction of 44% of doubling of the serum creatinine level ○ 55% lower relative risk of kidney replacement therapy
EMPEROR-Reduced[14]	Randomized, event-driven double-blind, parallel-group, placebo-controlled study	Efficacy and safety of once daily empagliflozin	Patients with chronic HFrEF	3730	Empagliflozin 10 mg versus placebo	• Empagliflozin group (versus placebo) had slower annual rate of decline in the estimated glomerular filtration rate (−0.55 versus −2.28 mL per minute per 1.73 m^2 of body-surface area per year, p<0.001)
VERTIS[36]	Randomized, double-blind, placebo-controlled multicentric study	CV outcomes with ertugliflozin in subjects with T2DM and established atherosclerotic cardiovascular disease	Patients with • T2DM • established ASCVD	8246	Ertugliflozin 5 mg versus ertugliflozin 15 mg versus matched placebo once daily (1:1:1)	• Ertugliflozin group (versus placebo) had lower risk of ○ death from kidney causes, kidney replacement therapy, or doubling of the serum creatinine level (HR, 0.81; 95.8% CI, 0.63 to 1.04) ○ death from CV causes (HR, 0.92; 95.8% CI, 0.77 to 1.11)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1C}, glycated haemoglobin; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

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observational study reported that 12% to 20% of patients with albuminuria and T2DM were untreated with any relevant recommended treatment within 6 months following the index diagnosis. Moreover, these patients are at greater risk of disease progression (microalbuminuric cohort: HR 1.31; 95% CI 1.08, 1.60; macroalbuminuric cohort: HR 1.44; 95% CI 1.21, 1.72; $p < 0.05$) than those with normoalbuminuria, suggesting a need for early intervention to prevent or delay disease progression.[58] The use of RAASi (hindering the excretion of potassium) along with impaired GFR, higher dietary potassium intake, and extracellular shift of potassium result in hyperkalemia being frequently reported among the users.[59–61] A retrospective study by Luo et al, reported U-shaped relationships between serum potassium levels and mortality and major adverse cardiovascular events.[62]

SGLT-2i such as dapagliflozin, offers a complementary pathway to the renin-angiotensin-aldosterone system inhibition to lower intra-glomerular pressure and protect nephrons.[63] Figure 3 presents the mechanism of action of RAASi and SGLT-2i. RAASi dilates efferent arterioles by decreasing the net filtration pressure, whereas dapagliflozin constricts the afferent arteriole,[55,64] thus complementing the RAASi mechanism of action.

Sequencing of SGLT-2i and RAASi

RAASi can be used to stabilize patients with CKD and hypertension according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[65] In patients with T2DM who are at a high-risk of cardiovascular or kidney disease, initiation of SGLT-2i is recommended as per the KDIGO and ESC guidelines irrespective of glycemic status.[51,65] The National Institute for Health and Care Excellence (NICE) guidelines also recommend the use of SGLT-2i as an add-on to RAASi, unless contraindicated, in individuals with eGFR of 25–75 mL/min/1.73 m^2 with T2DM or UACR of ≥22.6 mg/mmol.[66] If a patient does not have any high-risk conditions, both RAASi and SGLT-2i can be used together after educating the patient about hyperkalemia mainly due to RAASi treatment.

Recommended Treatment Algorithms

CKD is often associated with a high risk for major adverse cardiovascular events, HF, and all-cause mortality. This may have risk stratification implications for patients with T2DM, based on background CKD. Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin are recommended in patients with T2DM at risk of cardiovascular events to reduce hospitalization for HF, major cardiovascular events, ESKD, and cardiovascular death per 2021 ESC guidelines. Dapagliflozin, empagliflozin, or sotagliflozin are also recommended in patients with T2DM with and HF with reduced

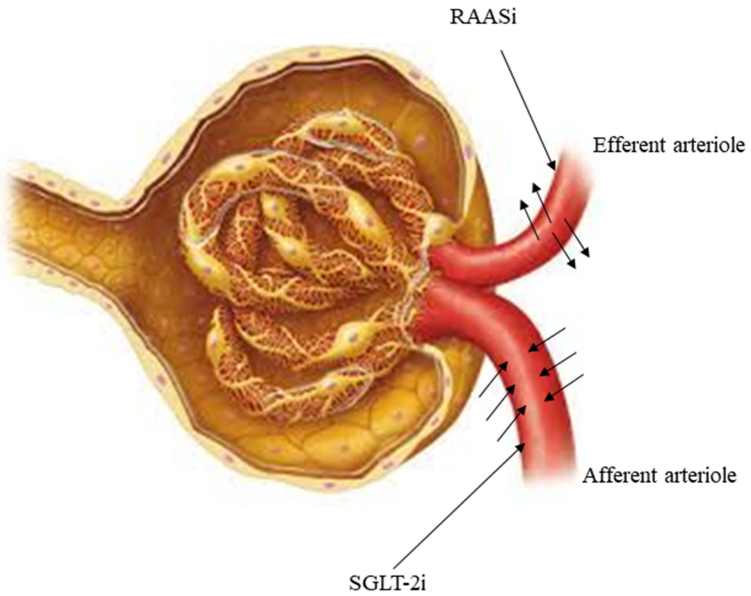

Figure 3 Mechanism of action of SGLT-2i and RAASi.
Abbreviations: RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

ejection fraction to reduce hospitalizations HF and cardiovascular death (2021 ESC guidelines).[51] Based on cardiovascular outcome trials, KDIGO and NICE guidelines recommend the use of SGLT-2i in patients with CKD with and without diabetes.[66,67] In patients with CKD with an eGFR ≥20 mL/min/1.73 m^2 and albuminuria with or without diabetes, the KDIGO guidelines recommend starting SGLT-2i, such as canagliflozin, empagliflozin, or dapagliflozin. If the eGFR falls below 20 mL/min/1.73 m^2 after initiating SGLT-2i, it may be continued for kidney protection unless it is not tolerated or kidney replacement therapy is initiated.[65,68] Figures 4 and 5 present the algorithm for the management of patients with hypertension and diabetic kidney disease, respectively.

In addition to RAASi and SGLT-2i, finerenone may also be administered to patients with CKD and T2DM. Data from the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial showed a reduced risk of CKD progression (HR, 0.82; 95% CI, 0.73 to 0.93; p=0.001) and cardiovascular events (HR, 0.86; 95% CI, 0.75 to 0.99; p=0.03) compared with placebo.[69] A systematic review and meta-analysis also demonstrated a similar result of lowering the risk of CKD progression (17.8% versus 21.1%) and cardiovascular risk (12.4% versus 14.2%) in patients with CKD and T2DM compared with placebo when finerenone was used as an add-on therapy to RAASi or SGLT-2i.[70] Finerenone acts as one of the novel tools for CKD with T2DM and offers a unique approach to further delay the CKD progression in these patients. It also provides an alternative treatment approach for patients who are unable to tolerate RAASi or SGLT-2i.

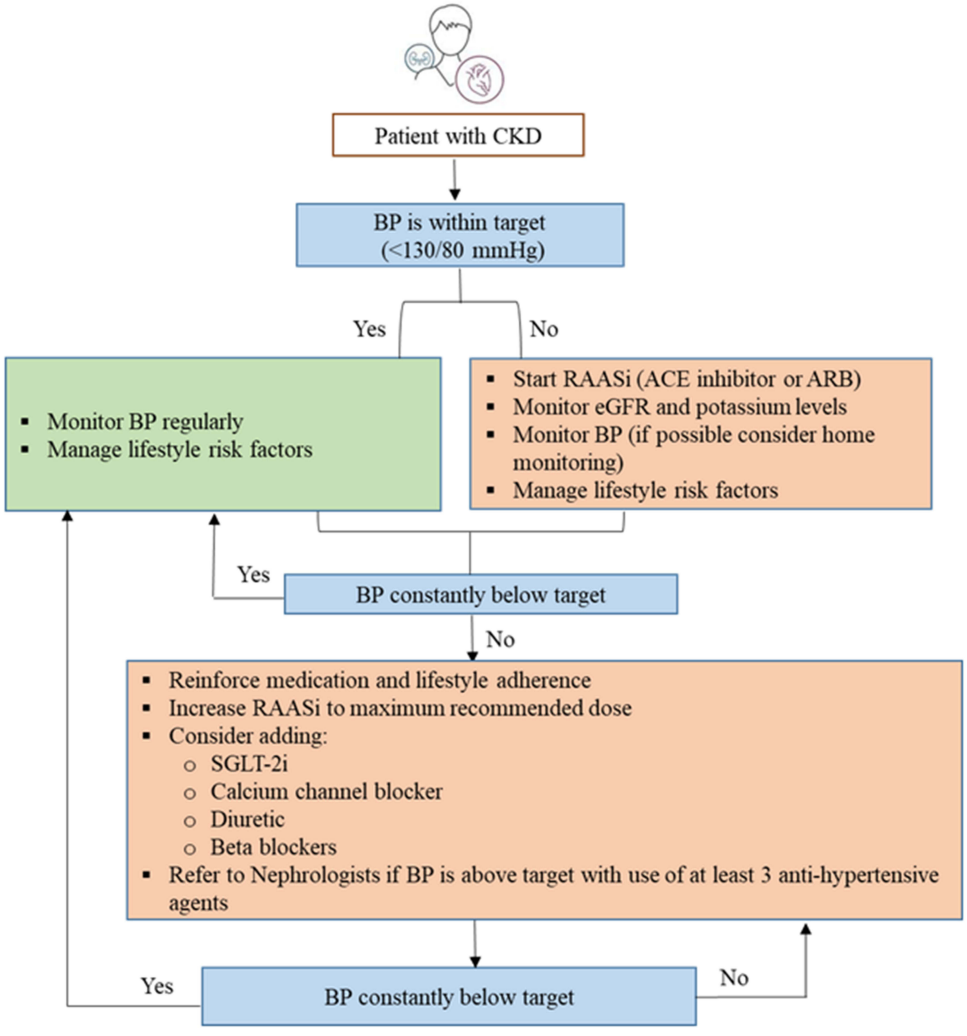

Figure 4 Algorithm for management of CKD in patients with hypertension.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

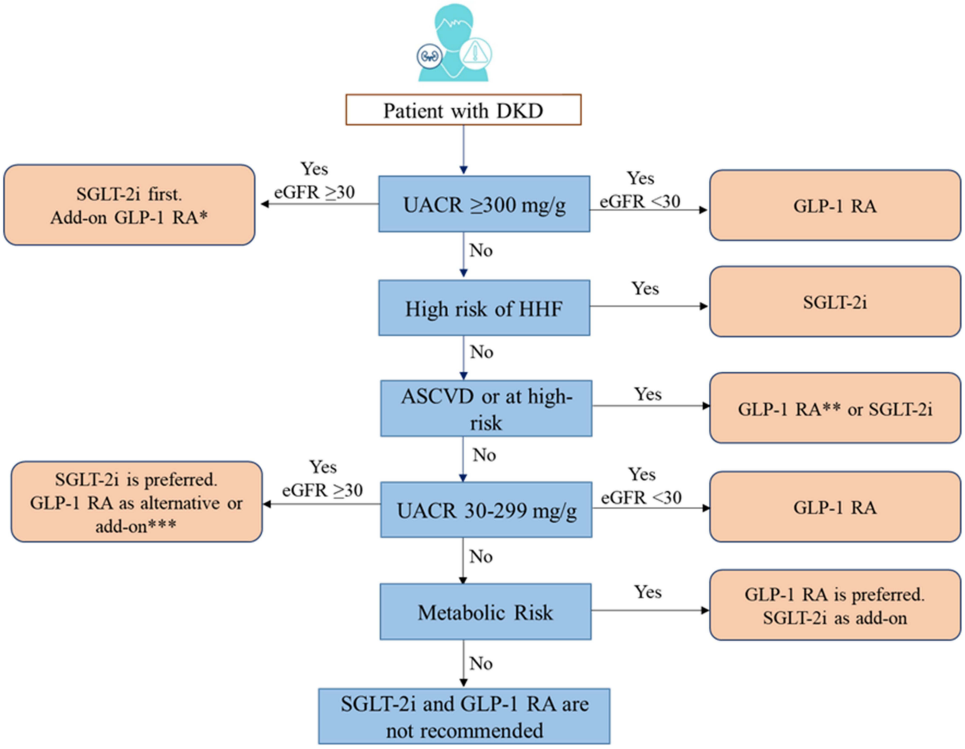

Figure 5 Algorithm for management of patients with DKD.
Notes: *Add-on GLP-1RA for uncontrolled metabolic risk. **GLP-1RA is preferred with coexisting uncontrolled metabolic risks. ***As an alternative if SGLT-2i is contraindicated and as an add-on for uncontrolled metabolic risks.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DKD, diabetic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalization for heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; UACR, urinary albumin-creatinine ratio.

Although the application of SGLT-2i have rapidly expanded, establishing them as a key therapeutic intervention in preventing CKD progression, an unmet need remains to reduce the residual risk in patients with renal or cardiovascular disease. Several studies have shown the efficacy of mineralocorticoid receptor antagonists and selective endothelin A receptor antagonists in patients with T2DM and CKD.[71,72] Future studies are required to explore the clinical benefits of combination therapy with SGLT-2i for reducing residual albuminuria and mitigate cardiovascular risk.[54,69] There is also scarcity of data on the efficacy and safety of SGLT-2i in transplant recipients and patients with ESKD. Other barriers for initiation of SGLT-2i are lower SGLT-2i prescription rate, presence of treatment inertia, unavailability, inaccessibility, unaffordability, time constraints, lack of continuity of care, and patients' perceptions and preferences need to be overcome.[73–76] Enhancing the knowledge of frontline primary care physicians and patients for cardiorenal benefits of SGLT-2i and risk control, addition of SGLT-2i by policymakers as crucial performance indicator along with glycemic control, adoption of multidisciplinary team-based care strategies, and providing access to financial assistance programs can improve the uptake of SGLT-2i for management of CKD.[37,76,77]

Conclusion

The burden of underdiagnosed and untreated CKD has assumed great proportions, primarily due to a lack of awareness of the condition among the general population and recent therapeutic advances in the healthcare community. DM and hypertension remain the most frequent causes, and patients with CKD often need to be treated for these comorbidities. SGLT-2i can play a significant role in CKD management in patients with or without DM because of its cardioprotective properties. Establishing nephrologist referral pathways, such as the SEARCH program, and creating guideline-based awareness about newer and novel therapeutic options in the healthcare community can help improve CKD management in MEA.

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Author Contributions

Ahmed Fathi ElKeraie conceptualized this study. All authors contributed equally to the literature review and the preparation of the first draft of the manuscript. All the authors contributed equally to study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, reviewing and editing the manuscript. All the authors have read and approved the final version of the manuscript to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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