The Role of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment Paradigm of Chronic Kidney Disease in Africa: An African Association of Nephrology Panel Position Paper

Faical Jarraya, Abdou Niang, Hussein Bagha, Elliot Koranteng Tannor, Ernest Kiswaya Sumaili, Davy Ip Min Wan, Mogamat-Yazied Chothia, Yewondwossen Tadesse Mengistu, Francois Folefack Kaze, Ifeoma Isabella Ulasi, Saraladevi Naicker, Mohamed Hany Hafez, Kouame Hubert Yao

PII: S2468-0249(23)01642-X

DOI: https://doi.org/10.1016/j.ekir.2023.12.019

Reference: EKIR 2580

To appear in: *Kidney International Reports*

Received Date: 13 April 2023

Revised Date: 29 November 2023

Accepted Date: 18 December 2023

Please cite this article as: Jarraya F, Niang A, Bagha H, Tannor EK, Sumaili EK, Min Wan DI, Chothia MY, Mengistu YT, Kaze FF, Ulasi II, Naicker S, Hafez MH, Yao KH, The Role of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment Paradigm of Chronic Kidney Disease in Africa: An African Association of Nephrology Panel Position Paper, *Kidney International Reports* (2024), doi: https://doi.org/10.1016/j.ekir.2023.12.019.

The Role of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment Paradigm of Chronic Kidney Disease in Africa: An African Association of Nephrology Panel Position Paper

Authors:

Faical Jarraya,[1] Abdou Niang,[2] Hussein Bagha,[3] Elliot Koranteng Tannor,[4,5] Ernest Kiswaya Sumaili,[6] Davy Ip Min Wan,[7] Mogamat-Yazied Chothia,[8] Yewondwossen Tadesse Mengistu,[9] Francois Folefack Kaze,[10] Ifeoma Isabella Ulasi,[11,12] Saraladevi Naicker,[13] Mohamed Hany Hafez,[14] Kouame Hubert Yao[15]

Affiliations:

[1]Sfax University, Faculty of Medicine, Nephrology Department and Research Lab LR19ES11, Sfax Tunisia. Email: jarraya_faical@yahoo.fr

[2]Nephrology Department, Dalal Jamm Hospital, Cheikh Anta Diop University, Dakar, Senegal. BP. 6548. Email: abdou.niang@ucad.edu.sn

[3]Department of Internal Medicine and Nephrology, M.P Shah Hospital, Nairobi, Kenya. Email: baghahussein@yahoo.com

[4]Department of Medicine, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [5]Renal Unit, Directorate of Medicine, Komfo Anokye Teaching Hospital, Kumasi, Ghana. Email: elliotktannor@yahoo.co.uk

[6]Renal Unit, Internal Medicine Department, University of Kinshasa, the Democratic Republic of Congo. Email: sumailiernest2015@gmail.com

[7]Nephrology Unit, SSR National Hospital, Pamplemousses, Mauritius. Email: ipdavy@hotmail.com

[8]Division of Nephrology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. Email: yaziedc@sun.ac.za

[9]Renal Unit, Department of Internal Medicine School of Medicine, College of Health Sciences Addis Ababa University, Addis Ababa, Ethiopia. Email: yewondt@yahoo.com

[10]Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon. Email: f_kaze@yahoo.fr

[11]Renal Unit, Department of Medicine, College of Medicine, University of Nigeria, Ituku-Ozalla, Enugu Nigeria; [12]Renal Unit, Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria. Email: ifeomaulasi@yahoo.co.uk

[13]Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. Email: saraladevi.naicker@wits.ac.za

[14]Professor of Medicine and Nephrology, Cairo University, Egypt; Past President of Egyptian Society of Nephrology and Transplantation (ESNT); President Elect African Association of Nephrology (AFRAN), Chair of Arab Board of Nephrology; Secretary General MESOT; Councilor DICG. Email: drhany_hafez@hotmail.com

[15]Department of Nephrology and Internal Medicine, University Hospital of Treichville, Felix Houphouet-Boigny University, Abidjan, Cote d'Ivoire. Email: yaohubert@yahoo.fr

Corresponding Author:

Faical Jarraya

Sfax University, Faculty of Medicine, Research Lab LR19ES11,

Avenue Majida Boulila, 3029 Sfax Tunisia

Email: jarraya_faical@yahoo.fr

ORCID: https://orcid.org/0000-0002-3619-3823

Running Title: Role of SGLT2i in CKD management in Africa

Keywords: Chronic kidney disease, Sodium-glucose cotransporter-2 inhibitors, SGLT2i, CKD management, Diabetic kidney disease, Africa

Abstract

Chronic kidney disease (CKD), a global public health problem, is increasing at an alarming rate across Africa. The increasing CKD burden in this region is mainly driven by a rapid surge in the prevalence of risk factors including diabetes, hypertension, obesity, and infectious diseases. To further aggravate the situation, CKD is known to progress rapidly to kidney failure (KF) in patients of African ethnicity. Given the serious health implications and prohibitively expensive treatment, it is paramount to focus on novel therapeutic prospects in CKD management to delay its progression to KF, prevent complications, and prolong survival. In recent years, substantial clinical and real-world evidence confirmed the cardiorenal protective benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with CKD, with or without diabetes. In this context, a steering committee meeting was convened with 13 key experts from the African Association of Nephrology (AFRAN) to discuss the epidemiology and magnitude of region-specific CKD burden, unmet needs and challenges, and implications of SGLT2i use in CKD management. This paper summarizes the expert views and opinions on the applicability of SGLT2is in different populations with CKD to support their safe implementation in clinical practice with a focus on reducing the CKD burden in the region.

1. Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by a loss of kidney function. It is defined as abnormalities of kidney structure and/or function, present for >3 months, with implications for health, and the presence of either estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 or markers of kidney damage, including albuminuria.[1] CKD is associated with high healthcare costs, poor quality of life, and serious adverse health outcomes (including cardiovascular disease [CVD], kidney failure [KF], infection, and death). As a major contributor to morbidity and mortality due to non-communicable diseases, CKD is ranked as the 10th leading cause of death worldwide, with an estimated worldwide prevalence ranging from 10% to 16%.[2,3] Currently, more than 850 million people have kidney disease, the vast majority of whom are living in low and middle-income countries with limited access to healthcare resources.[4]

Africa is witnessing a high and rapidly increasing incidence of cardio-metabolic diseases, which are leading contributors to deaths due to non-communicable diseases in this region. The significant increase in the prevalence of hypertension, type 2 diabetes mellitus (T2DM), endemic infections such as HIV, hepatitis B and C, tuberculosis, and malaria as well as the use of herbal medications and other nephrotoxins are projected to drive the burden of CKD in Africa.[5]

CKD is also a significant risk factor for CVD. Patients with CKD have a higher propensity to develop coronary artery disease, heart failure, arrhythmias, and sudden cardiac death.[6] CVD associated with CKD is more likely to cause higher mortality rates than KF alone.[7,8] Cardiovascular (CV) events contribute to a large proportion of unfavorable outcomes in patients with CKD.[9] Conventional CV risk factors such as hypertension, T2DM, and dyslipidemia are highly prevalent in patients with CKD and contribute to atherosclerotic cardiovascular disease

(ASCVD), particularly in earlier CKD stages. Reducing CV risk in patients with CKD is imperative for any CKD management strategy.

Currently, CKD accounts for 4 million disability-adjusted life years (DALYs) lost annually across the African continent, marginally lower than T2DM (6.4 million DALYs).[10] It is estimated that by 2030, more than 70% of patients with KF would be living in low-income countries, such as those in Sub-Saharan Africa (SSA).[11,12]

The true prevalence and disease burden of CKD in Africa remains unknown due to multiple factors ranging from a paucity of epidemiological data to a lack of standardization of diagnostic and staging tests for kidney damage assessment. Accurate estimation of the prevalence and disease burden of CKD is a cost-effective approach to draw government and policymakers' attention to the exponential rise of CKD in this region, and encourage efforts towards prevention, detection, and treatment of CKD at earlier stages.

Several practical challenges are unique to Africa, which undermine optimal kidney care for patients with CKD. Financial feasibility, clinical and ethical optimization of dialysis services, and lack of uniform and consistent distribution are other significant challenges to KF care.[13] Owing to financial constraints, currently existing CKD management strategies include lifestyle modifications (weight control, dietary restrictions, exercise, and smoking cessation), maintaining target levels of blood pressure and blood glucose, avoiding exposure to nephrotoxins, and pharmacological intervention with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB). Although newer therapeutic agents such as sodium-glucose cotransporter-2 inhibitors (SGLT2is) have demonstrated kidney protective benefits and in associated conditions of T2DM and CVD, their use remains limited due to high cost and accessibility issues in this region.[14] Preventing progression to KF is thus of paramount importance. Preventive strategies to

reduce the overall risk of CKD development in healthy individuals (primary prevention), early identification of CKD and its risk factors and prompt treatment initiation (secondary prevention), and prevention of precipitating factors in advanced stages of CKD (tertiary prevention) can considerably delay the progression to KF and requirement of kidney replacement therapy (KRT).[15]

This position paper intends to provide an overview of the available region and country-specific prevalence and disease burden of CKD along with the barriers in the management strategies of CKD in the African region. The paper also summarizes the current evidence on the role of SGLT2is and its applicability in different populations with CKD to support their safe implementation in CKD management.

2. Methodology

A steering committee meeting was convened in November 2022 to discuss the current unmet needs and challenges in nephrology practice for CKD management in the region. A panel comprising 13 key external experts in the field of nephrology from 5 African regions: center African region (Cameroon, the Democratic Republic of Congo), west African region (Senegal, Ghana, Cote d'Ivoire, Nigeria), east African region (Ethiopia, Kenya), austral African region (Mauritius, South Africa), and north African region (Egypt, Tunisia) congregated to discuss the prevalence and regional burden of CKD, evaluate risk factors on incidence and progression of CKD, and identify gaps in effective screening, diagnosis, and management of CKD in this region. Based on emerging clinical evidence about the effectiveness of SGLT2is in slowing the risk of progression of CKD to KF, the panel also reviewed the current clinical trial evidence of SGLT2is and its implications in the African region. The panel proposed recommendations for their implementation as first-line nephroprotective agents in an effort to reduce the high burden of kidney disease in the region.

The panel is a representation of the key experts and members of the AFRAN society. The experts were from the 12 countries as mentioned in the methodology, however the evidence presented on the CKD prevalence, burden, epidemiology, current practices and challenges can be generalized to the entire African region and the recommendations provided can be adapted across the continent.

The recommendations presented in this position paper are an outcome of open discussion among the experts based on their clinical experience in CKD patient care, supported by published evidence on cardiorenal outcomes of SGLT2is.

3. Prevalence and Disease Burden of CKD in Africa

Epidemiological studies on the incidence, prevalence, and disease burden of CKD are sparse across Africa and it is probably underestimated and largely unknown. A systematic review and meta-analysis of 21 medium-quality and high-quality studies in 2014 found the overall prevalence of CKD to be 13.9% (95% confidence interval [CI], 12.2–15.7).[16] The International Society of Nephrology Global Kidney Health Atlas - Africa initiative reported the overall prevalence of CKD in Africa to be 6.28%, with wide variability within countries such as Mauritius, an upper-middle income country, reporting the highest prevalence as 17.63%, and Uganda, a low-income country, reporting the lowest prevalence (4.87%).[17] A systematic review and meta-analysis published in 2018 reported the prevalence of CKD stages 1 to 5 in the general population of Africa as 15.8% (95% CI, 12.1–19.9), and 4.6% (95% CI, 3.3–6.1) for CKD stages 3 to 5.[18] The prevalence was significantly higher in SSA compared to North Africa for both CKD stages 1 to 5 (17.7%; 95% CI, 13.7–22.1, vs 6.1%; 95% CI, 3.6–9.3) and CKD stages 3 to 5 (4.8%; 95% CI, 3.2–6.6, vs 2.6%; 95% CI, 2.3–2.9).[18] The highest prevalence of CKD (19.8%) was seen in West African countries

[Fig 1].[19] The overall prevalence of all stages of CKD in the high-risk populations was 32.3%—the highest with hypertension (35.6%), followed by diabetes (32.6%) and HIV (27.3%).[18] The mortality rate attributable to CKD ranged from 0.57% in Zambia to 10.36% in Mauritius, and the percentage of DALYs ranged from 0.58% in Nigeria to 6.85% in Mauritius.[17] Another systematic review assessing CKD burden among the African general population and high-risk groups reported a prevalence that ranged from 2% to 41% (pooled prevalence: 10.1%; 95% CI 9.8% to 10.5%) with higher prevalence in high-risk groups such as HIV, T2DM and hypertension.[20] A systematic review and meta-analysis of 12 African studies that included 5297 participants from 6 countries (Ghana, Nigeria, Uganda, Tanzania, Democratic Republic of Congo, and South Africa) found the pooled prevalence of CKD in hypertensive patients to be around 17.8% (95% CI, 13.0–23.3) with the highest prevalence seen in West Africa (21.3% [95% CI, 16.1–27.0]). resulting in almost and an 4 times higher incidence of KF when compared to Caucasians. [21,22]

A recent study in Senegal showed a CKD prevalence of 5.2% with almost 92% of the patients being diagnosed with advanced stages of CKD, and 34.9% with KF.[23] Similarly, in another study conducted at a teaching hospital in the southeast of Nigeria, KF cases accounted for 7.96% of all medical admissions and 41.69% of renal admissions.[24] The Maremar (Maladies rénales chroniques au Maroc) study conducted in Morocco estimating the prevalence of CKD, hypertension, diabetes, and obesity in a randomized, representative, high response rate (85%) sample found a low prevalence of CKD (2.9% adjusted to the actual adult population of Morocco).[25] Another concerning finding of a large community-based study on CKD prevalence in SSA was a CKD prevalence of 6.8% in a community where the mean age of the adult population was 38 years, with a wide variation between regions. The CKD prevalence was primarily estimated by high prevalence of proteinuria with largely preserved kidney function.[26]

Fabian et al through their population cohorts studies from Malawi, Uganda, and South Africa demonstrated that estimating glomerular filtration rate using serum creatinine substantially underestimated the individual and population-level burden of impaired kidney function in Africa highlighting the need for scalable and affordable ways to accurately identify impaired kidney function in Africa.[27]

Across all three countries, creatinine-based GFR-estimating equations were inadequate that worsened with declining kidney function. eGFR equations overestimated the proportion grade 1 CKD compared with measured GFR and underestimated the proportion with grade 2 to 5 stages of kidney function. Creatinine-based equations underestimated stages grade 2 to 5 stages by at least 50%. Overestimation of individual GFR and misclassification by GFR stage was exacerbated when using ethnicity coefficients for the MDRD and CKD-EPI equations. GFR estimation using cystatin C alone or in combination with creatinine led a reduction in the overestimation of mGFR when compared with creatinine-based estimates that implied that the estimates of prevalence of impaired kidney function using cystatin C were more than two-times higher than creatinine-based estimates.[27]

The cost of non-dialysis management and KRTs are substantially higher in SSA than in North Africa and is mainly privately funded or out of pocket.[17] A majority of African countries do not have the provision of kidney transplants and thus rely heavily on dialysis. Although both hemodialysis (HD) and peritoneal dialysis (PD) are available, HD is more commonly used and only 41% of countries have PD facilities.[17] The annual costs of HD and PD were generally more than US$10 000 higher in SSA than in North Africa. The availability of healthcare resources and workforce in the Africa region are also considerably limited as compared to global estimates with an average of 0.62 nephrologists per million population (pmp), compared with 9.95 pmp

globally.[17] Most patients with KF initiate dialysis in Africa but discontinue soon after due to unsustainable treatment costs and insufficient infrastructure, thus further increasing the disease burden and complications associated with KF.[28]

4. CKD Etiology and Risk Factors

The recent epidemiological transition resulting in a surge of non-communicable diseases such as T2DM, hypertension, and obesity is adding to the growing prevalence rate of CKD in the African region.[16,29] CKD progression is also known to be accelerated in patients of African origin due to non-modifiable risk factors such age, gender and genetic susceptibility to hypertension, higher frequencies of Apolipoprotein L1 (*APOL1*) G1 and G2 high-risk alleles.[30–32]The prevalence of hypertension in Africa is estimated to be around 36% and continues to grow rapidly.[33] The pathogenesis of hypertension varies significantly in the African population with a propensity for a more aggressive course of hypertension resulting in early target organ damage. Several factors contribute to this phenomenon including genetic polymorphisms, low-birth weight, aberrant salt sensitivity, and poor socio-economic conditions.[34–36] Another significant risk factor associated with CKD highly prevalent in the African region is hypertensive disorders of pregnancy, predominantly pre-eclampsia and eclampsia. [37] Coupled with inadequate access and low quality of antenatal care, preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality in the African region. Early pre-clinical studies have demonstrated decrease in blood pressure and natriuresis due to SGLT2is thus ameliorating the long term CV risk associated with pre-eclampsia.[38]

Autosomal dominant polycystic kidney disease (ADPKD), the most common form of hereditary kidney disease, is noted as another significant cause of CKD in Africa.[39] In a 13-year retrospective

hospital-based study (2005–2017), ADPKD was identified as the fourth leading cause of CKD among Ghanaian adults.[40]

Approximately 24 million adults were reported to have diabetes in Africa in 2021. This figure is estimated to increase to 33 million by 2030 and 55 million by 2045.[41] Uncontrolled T2DM is an established modifiable risk factor for CKD, and also accelerates disease progression. Obesity is not just an initiating risk factor for the development of CKD, but it also leads to CKD progression.[19] In a study evaluating the prevalence of undiagnosed CKD in SSA, the prevalence of CKD was found to be 36%, with 16% of them being obese individuals. Obesity ranked as a top risk factor after hypertension (44%) and diabetes (39%).[42]

Glomerular diseases are one of the most common causes of the progression of CKD. Studies from Africa have shown that glomerular diseases (primary and secondary) account for 10.2% to 52% of patients with KF.[43] Chronic glomerulonephritis related to endemic or neglected infectious diseases remains the major cause of CKD in Africa.[44] Consequently, the only sign of CKD for those patients at an early stage is urinary abnormalities such as hematuria and proteinuria.

Communicable diseases such as HIV and hepatitis B and C contribute significantly to the large burden of CKD in SSA. The prevalence of CKD in HIV-positive individuals ranges from 22.9% to 51.8% as per some studies conducted in Nigeria with one of the highest prevalences of HIV in Africa.[45–47] The prevalence of CKD in HIV-positive patients, naïve to antiretroviral therapy, was reported to be 13.4% in another Nigerian study.[48] A systematic review of published literature from 60 countries reported a prevalence of 7.9% (95%CI 5.2-11.1%) in the African region.[49] HIV-associated nephropathy is known to be the most severe form of HIV and kidney disease and a leading cause of KF characterized by the presence of focal glomerulosclerosis.[50–52]

Hepatitis B prevalence in SSA is also amongst the highest in the world, varying between 5% to 20%.[53,54] In a retrospective study of patients with CKD screened for hepatitis B surface antigens and hepatitis C antibodies, the seroprevalence of hepatitis B and hepatitis C, and coinfection was seen in 15.6%, 4.8%, and 0.9% of the patients, respectively.[55] Parasitic and protozoal infections such as schistosomiasis, filariasis, leishmaniasis, and malaria are endemic to SSA. Exposure to nephrotoxins also adds to the burden of CKD. The spectrum of kidney disease caused by infectious etiologies varies widely from acute kidney injury (AKI), acute and chronic glomerulonephritis, and interstitial nephritis to pyelonephritis. Infections have been implicated in many adverse kidney syndromes, including CKD of unknown etiology.[56]

5. Current Management of CKD

Patients with advanced CKD are more susceptible to developing adverse outcomes, including CKD progression, CV complications, and KF. Early identification of CKD and its accurate staging would enable the implementation of appropriate interventions to delay its progression and reduce the risk of CV complications. For effective CKD management, a comprehensive multidisciplinary approach is recommended to target risk factors for CKD with lifestyle changes (dietary management, physical activity, weight control, and abstinence from smoking) along with optimal management of co-morbid T2DM, hypertension, and associated CV risk factors. Additionally, patients require regular monitoring for complications of CKD, such as anemia, acid-base and electrolyte imbalances, and mineral bone diseases **[Fig 2]**.[1,57,58] Persistently elevated serum creatinine and albuminuria are important diagnostic and prognostic biomarkers of CKD. For initial assessment, measurement of eGFR using serum creatinine is considered the gold standard because of its affordability, easy accessibility and long history of clinical use. Measurement of albuminuria

by a spot urine sample using either albumin-specific dipsticks or urine albumin-to-creatinine ratio (UACR) are most accepted by physicians and nephrologists. KDIGO preferentially recommends using UACR, followed by urine protein-to-creatinine ratio (uPCR) over total protein urinalysis strips (either automated or manual) in assessing albuminuria in CKD diagnosis and follow-up. Although quantitative assessment of albuminuria using UACR is favored and recommended by the guidelines, it is unaffordable in African countries and use of urine test strips such Albustix and dipstick screening is considered acceptable in the absence of more reliable methods and be followed by appropriate confirmatory testing.

In the current clinical practice, the use of renin-angiotensin-aldosterone system (RAAS) blockers (including ACEi/ARB) are the mainstay for delaying CKD progression and managing complications. In view of their proven efficacy in terms of improvement in albuminuria and hypertension, the Kidney Disease Improving Global Outcomes (KDIGO) 2021 guideline for the management of blood pressure in patients with CKD recommends using ACEi or ARB as first-line therapeutic agents for patients with hypertension, CKD, and moderate to severe albuminuria (G1 [$\geq$ 90 ml/min/1.73m^2] to G4 [15–29 ml/min/1.73m^2], A2 [30-300 mg/g] and A3 [>300 mg/g]), with or without T2DM.[58]

Despite their established renoprotective efficacy for significant risk reduction (in terms of doubling of serum creatinine, KF, and death) by 16% and 20%, as reported by RENAAL[59] and IDNT[60] studies, respectively, there is a continued residual risk of progression of CKD to KF or premature death from CV events. These findings highlight the need for novel medications to address this continuing risk.

6. Emerging Role of Sodium-glucose Cotransporter-2 Inhibitors in CKD

SGLT2is are a novel group of glucose-lowering agents with the mechanism of action based on the inhibition of sodium-glucose cotransporter-2 in the proximal convoluted tubule preventing reabsorption of glucose, thereby causing increased urinary excretion of glucose and sodium.[61] This results in a multitude of metabolic benefits and positive clinical outcomes, such as a reduction in glycosylated hemoglobin (HbA1c), albuminuria, body weight, and blood pressure **[Fig 3]**.

With emerging evidence, SGLT2is have transformed the management of CKD in patients with and without T2DM. The primary mechanism by which SGLT2is are thought to be nephroprotective is through increasing distal sodium delivery and inhibiting tubuloglomerular feedback resulting in afferent arteriole vasoconstriction and reduction in intraglomerular pressure. Current indications for SGLT2is include T2DM, heart failure, and CKD **[Table 1]**.[62,63]

Summary of Efficacy of SGLT2is

Most cardiovascular outcome trials (CVOTs) on SGLT2is were not specifically intended to evaluate kidney outcomes. However, they analyzed them as secondary endpoints, and therefore, were underpowered to validate renoprotective benefits of SGLT2is. Despite insufficient power and a relatively low percentage of patients with advanced-stage CKD in these trials,[64] most CVOTs demonstrated the renoprotective efficacy of SGLT2is in patients with T2DM. Favorable kidney outcomes from the CVOTs paved the way for subsequent clinical studies evaluating the effect of SGLT2is on primary kidney-specific endpoints in patients with CKD including the recent landmark EMPA-KIDNEY trial that included a heterogeneous patient cohort with substantial representation of patients with non-diabetic kidney diseases (UACR <30 mg/g; eGFR ≤20 mL/min/1.73 m^2) **[Table 2]**.

Real-World Kidney Outcomes with SGLT2is

Consistent with the results from major clinical trials and CVOTs, several real-world effectiveness studies have generated evidence in favor of cardiorenal protective benefits of SGLT2is in T2DM patients followed up under routine clinical care.[65,66] In a real-world multinational CVD-REAL 3 observational cohort study involving 65 231 T2DM patients who received propensity-matched treatment with SGLT2is and other glucose-lowering agents, SGLT2i treatment reduced the annual rate of eGFR decline by 1.53 ml/min per 1.73 m^2 (95% CI, 1.34–1.72; $P < 0.0001$). During the mean follow-up duration of 14.9 months, patients treated with SGLT2is had a lower risk of composite kidney events, compared to other anti-diabetic medicines (hazard ratio [HR], 0.49; 95% CI, 0.35–0.67; $P < 0.0001$).[67] Similar findings emerged from another observational study based on the Japanese CKD registry with lower risk of occurrence of composite kidney outcome (50% eGFR decline and KF), regardless of the rate of eGFR decline or presence of proteinuria at baseline.[65] Further, the antiproteinuric effect of SGLT2is was first confirmed by the DARWIN-T2D study which reported a noticeable decline in median urine albumin excretion rate (AER) following 6 months of treatment with dapagliflozin, compared to no change in AER with the comparator drugs.[68]

SGLT2i have been shown to prevent decline in kidney function through reduction in glomerular hypertension independent of their effect on glycemic control.[69,70] A real-world study analyzed kidney outcomes in 4446 patients with diabetic kidney disease (DKD) treated with SGLT2is compared to standard anti-diabetic and renoprotective medications. In this study, patients prescribed SGLT2is showed a significant reduction in CKD progression (HR, 0.60; 95% CI, 0.49–0.74) and risk of developing KF (HR, 0.33; 95% CI, 0.17–0.65), with more pronounced beneficial effects seen in moderate to advanced CKD stages.[71] A theoretical extrapolation based

on CREDENCE trial data is that a hypothetical trial participant aged 63 years with a baseline eGFR of 56 ml/min/1.73 m^2 is likely to develop KF in the next 10 years, with an annual rate of eGFR decline of 4.6 ml/min/year with only RAAS blockade. However, adding SGLT2is to the ongoing RAAS blockers would reduce the rate of eGFR decline to only 1.85 ml/min/year, thus further delaying the risk of developing KF by 15 years, even after adjusting for the initial dipping of eGFR **[Fig 4]**.[70] Long-term results from the DAPA-CKD trial extrapolated over a 10-year period found that patients receiving dapagliflozin spent a longer duration in CKD stages 1–3 (0.65 [95% CI, 0.41–0.90] years per patient) and shorter period in stages 4–5 (-0.23 [95% CI, 0.45–0.00] years per patient) compared with those on placebo. Additionally, dapagliflozin treatment prevented 83 deaths and initiation of KRT in 51 cases per 1000 patients over 10 years with a reduction in predicted rates of hospitalizations due to HF and instances of sudden decline in kidney function by19 and 39 estimated events per 1000 patients, respectively.[72] The EMPA-KIDNEY trial included adults with or without T2DM with eGFR 20-45 ml/min/1.73 m^2 regardless of albuminuria or eGFR 45-90 ml/min/1.73 m^2 with UACR ≥200 mg/g on maximally-tolerated RAAS blockade.[69,73,74] Unlike the DAPA-CKD trial, the EMPA-KIDNEY encompassed a larger representation of patients within the G2A2 CKD subgroup, thereby extending the SGLT2i intervention to patients with lower risk and higher eGFR.[69,73,74] Notably, EMPA-KIDNEY demonstrated lower utilization of RAAS blockade and included a more substantial representation of non-diabetic kidney diseases, encompassing over 1600 participants with glomerular disease, more than 1400 with hypertensive kidney disease, over 450 with tubulointerstitial disease, and more than 600 with an unknown cause.[73] The EMPA-KIDNEY trial was stopped early in March 2022 for efficacy suggesting that CKD patients without

albuminuria also benefitted from SGLT2i thereby expanding the population eligible for SGLT2i therapy.[69,73,74]

Using the data from CREDENCE and FIDELIO trials, a recent study by Heerspink et al revealed that combined treatment with SGLT2is and mineralocorticoid-receptor antagonists (MRAs) in patients with T2DM and CKD could prolong the event-free survival up to 16.7 years at the age of 50 years, compared with 10 years using only RAAS blockers.[75] These trial data corroborated findings from the CRIC trial that showed an incremental gain in event-free survival of 6.3 years (95% CI, 5.2–7.3) on combined treatment with SGLT2i and MRA.[76]

Cost-effectiveness of SGLT2is

SGLT2is have recently been added to the WHO's Model Essential Medicines List; that target prices to achieve common thresholds for cost-effectiveness or cost-savings achievable with nominal price reductions. An extensive review conducted recently that aimed to estimate price targets to guide negotiations for inclusion in national formularies post the addition of SGLT2is to WHO's Essential Medicines List found that they would need to have a median price of $224 per person per year (a 17·4% cost reduction; IQR $138–359, population-weighted across countries; mean price $257).[77] There is currently limited data on cost analysis of SGLT2is in the African continent due to reasons ranging from a delayed introduction of the agents in Africa and limiting costs to inequitable access. Despite the benefit of SGLT2is on primary and secondary prevention of complications and risk factors associated with CKD, the health economic impact of SGLT2i especially in LMICs remains unclear. Studies conducted thus far on the socio-economic impact of initiating with an SGLT2i have shown decreased medical costs and increased the QALY compared with conventional treatment establishing the economic benefit.[78] Another significant concern is the availability of resources and co-payments within public health-care systems in Africa, resulting

in continued endorsement and listing of older therapies rather than funding newer medications such as SGLT2is.

Use of SGLT2i in Pediatric Population

Although safety and efficacy data of SGLT2is in children with CKD is limited, they are generally well tolerated and not associated with any unexpected or clinically significant safety findings in the pediatric population with type 2 diabetes mellitus in the studies conducted so far.[79,80] They are proven effective in children with inherited proteinuric CKD with an eGFR >60 ml/min per 1.73 m^2. [81,82] However further studies in larger populations with long term follow-up are necessary.

7. Important Practical Considerations for Prescribing SGLT2i Therapy in CKD

Initial Decline in eGFR after SGLT2i Initiation

SGLT2i initiation induces a reduction in eGFR (~3 to 5 ml/min/1.73m^2) during the first 2 to 4 weeks of treatment, which is short-lived and starts normalizing by 12 weeks, followed by an attenuation of the slope of eGFR decline.[83–86] This effect is mainly attributed to positive hemodynamic changes and correlated with long-term preservation of kidney function. Evidence from randomized clinical trials (RCTs) suggests that SGLT2i users have a slower annual rate of eGFR decline, compared to the steady decline observed with non-users, conferring long-term renoprotective benefits **[Table 3]**.[83,86,87]

Risk of Hypoglycemia

Reduced kidney function may increase the risk of hypoglycemia.[88] The glucose-lowering effect of SGLT2is is insulin-independent; their use is associated with a lesser risk of hypoglycemia in patients with CKD and T2DM, compared to other anti-hyperglycemic agents (sulfonylureas).[89]

Consistent with these findings, DAPA-CKD, CREDENCE and EMPA-KIDNEY trials showed no increased risk of hypoglycemia in patients with CKD and T2DM.[83,90,91] In the context of dose adjustment of concomitant anti-diabetic medications, the clinicians must consider that the glucose-lowering efficacy of SGLT2is is reduced at lower eGFR levels (below 30 ml/min per 1.73 m^2).[92]

Risk of Hyperkalemia

Use of RAAS blockers are known to increase the risk of hyperkalemia leading to discontinuation.[93] Data from the *post hoc* analysis of the CREDENCE trial showed that treatment of patients with T2DM and CKD with canagliflozin reduced the incidence of hyperkalemia or initiation of potassium binders compared to placebo (32.7 vs. 41.9 participants per 1000 patient-years; HR, 0.78; 95% CI, 0.64–0.95; $P = 0.014$) with no effect on the risk of hypokalemia (HR, 0.92; 95% CI, 0.71–1.20; $P = 0.53$).[94] A subsequent meta-analysis involving six randomized double-blind trials evaluated the effects of SGLT2i on serum potassium levels in patients with T2DM at high CV risk or with underlying CKD The findings revealed a reduction in the overall risk of serious hyperkalemia (HR, 0.84; 95% CI, 0.76–0.93; $P_{heterogeneity} = 0.71$) with no variations in risk observed across different levels of baseline kidney function, history of HF, and utilization of MRA and diuretic agents. Furthermore, the use of SGLT2is did not elevate the risk of inducing hypokalemia (HR, 1.04; 95% CI, 0.94–1.15; $P_{heterogeneity} = 0.42$).[95] These findings align with a meta-analysis of the CANVAS Program, indicating that the use of canagliflozin had no significant impact on serum potassium levels across the general population, regardless of dosage, RAAS inhibitors use, or baseline eGFR levels. Moreover, the frequency of hyperkalemia-related adverse events were similar with canagliflozin and the placebo use.[96] Additionally, a cross-over, randomized clinical trial investigating the effects of dapagliflozin and the selective MRA eplerenone in patients with T2DM and CKD, both individually and in combination showed a higher incidence of hyperkalemia

in patients receiving eplerenone alone (n=8; 17.4%) compared with dapagliflozin and eplerenone combination therapy. Hence, SGLT2is may present a viable option for patients who are unable to tolerate RAAS blockers due to hyperkalemia.

Patients with Stage 4 CKD

In a prespecified analysis of the DAPA-CKD trial that included 624 patients with stage 4 CKD at baseline (eGFR: 25 to 30 ml/min per 1.73 m^2), the use of dapagliflozin resulted in 27% reduction in primary composite efficacy endpoint (≥50% sustained decline in eGFR, KF, or death due to kidney or CV causes) and significant decrease of eGFR slope decline over time (2.15 ml/min per 1.73 m^2 with dapagliflozin vs 3.38 ml/min per 1.73 m^2 with placebo). These findings were in agreement with those reported for the overall dataset comprising a larger population with stages 2 or 3 of CKD. Additionally, no increase in the rate of adverse events was observed for this sub-population. SGLT2i treatment was continued even after eGFR declined to <15 ml/min per 1.73 m^2.[97] Consistent with these results, the EMPEROR-reduced trial demonstrated similar beneficial effects of empagliflozin on CV and kidney endpoints across all eGFR categories, extending even in patients with eGFR <30 ml/min per 1.73 m^2.[98] Therefore, SGLT2is comprise a beneficial addition to the therapeutic armamentarium for patients with CKD, particularly for earlier stages although studies have also shown benefits in case of late stage CKD.[99,100]

Chronic Glomerulonephritis

Results from a subgroup analysis of DAPA-CKD trial participants with focal segmental glomerulosclerosis (FSGS)[101] and IgA nephropathy[99] revealed positive outcomes in terms of substantial reduction in annual mean rate of chronic decline of eGFR with dapagliflozin, compared with placebo.

In 104 biopsy-confirmed FSGS patients, dapagliflozin reduced the rate of primary composite kidney outcome (sustained eGFR decline ≥50%, KF, or kidney or CV death) compared with placebo (HR, 0.62; 95% CI, 0.17–2.17). The annual rate of eGFR decline was found to be slower in the dapagliflozin group (-1.9 ml/min/1.73 m^2, 95% CI, -3.0, -0.9) versus placebo (-4.0 ml/min/1.73 m^2, 95% CI, -4.9, -3.0) resulting in a between-group difference of 2.0 ml/min/1.73 m^2/year (95% CI, 0.6–3.5).[101]

Among 270 patients with IgA nephropathy, only 6 (4%) dapagliflozin-treated patients reached the same primary composite kidney outcome compared to 20 (15%) in the placebo arm (HR, 0.29; 95% CI, 0.12–0.73) during the median follow-up period of 2.1 years. Additionally, the mean rate of eGFR decline with dapagliflozin was -3.5 ml/min/1.73 m^2/year relative to -4.7 ml/min/1.73 m^2/year with placebo. Furthermore, dapagliflozin reduced the urine albumin-to-creatinine ratio (UACR) by 26% relative to placebo.[99] Results from subgroup analysis from the EMPA-CKD trial, including 25% of patients with non-diabetic glomerulonephritis, are awaited.[91]

Kidney Transplant Recipients

Although there is a scarcity of published evidence, SGLT2i therapy in patients with kidney transplants demonstrated a modest effect on improving glycemic control, and body weight with reassuring safety data, in particular on the risk of urinary tract infection (UTI). There is reported evidence of a physiologic dip in eGFR consistent with an appropriate hemodynamic response and reduction in hyperfiltration which remains intact in kidney transplant recipients and is likely to translate to long-term renoprotective benefit.[102] A very recent retrospective cohort study including 226 kidney transplant SGLT2i users showed a significant reduction in the risk of the composite primary outcome of all-cause mortality, graft loss, and doubling of creatinine in diabetic kidney

transplant patients than the control group in the multivariate and propensity score-matched models (adjusted HR, 0.43; 95% CI, 0.24–0.78; *P* = 0.006 and adjusted HR, 0.45; 95% CI, 0.24–0.85; *P* = 0.013, respectively).[103]

8. Critical Barriers in Effective CKD Care and Optimal Initiation Of SGLT2i in Africa

Multiple barriers prove to be hindrances in the implementation of effective screening programs and management of CKD in the African region. Social risk factors, such as limited financial resources and low health literacy are significant patient-level barriers. There are no CKD registries or real-world data from the region. Unavailability of educational materials especially in the rural areas, lack of regional data leading to application of western guidelines in a population that is markedly different in racial, ethnic, and socio-cultural profile, inadequate medical reimbursements and insurance schemes and sub-optimal patient adherence to follow-up are major challenges in CKD care pathways.

Despite the clinical practice guideline recommendations and high-quality published evidence supporting the cardiorenal protective effects of SGLT2is, their utilization remains dismally low in real-world clinical scenarios. As is the case with several novel therapies that conventionally take an average of 17 years from research to implementation in clinical practice, SGLT2is are also faced with several barriers to effective adoption to practice.[104] Limited insurance coverage, lack of knowledge especially regarding side effects, poor accessibility, high out of pocket expenditure, and prescriber inertia were cited by the experts as potential barriers to adopting SGLT2i therapy in the African setting. Changing clinical practice and overcoming "prescriber inertia" requires comprehensive coordination between patients, physicians, and healthcare systems through a targeted approach.[105] Despite the fact that patients of African ancestry are genetically predisposed

to accelerated CKD progression, most of the SGLT2i trials published to date only enrolled few patients with black ethnicity. The distinct effects of SGLT2i in black and in African populations if any have not been researched. Given the overwhelming racial disparity for CKD risk and progression in black patients, the key experts recommended undertaking future RCTs to validate clinical outcomes with SGLT2is in African populations.

From 2015 to 2019, despite an increasing trend for SGLT2i use for T2DM treatment (3.8% to 11.9%), their overall use was relatively lower among patients with ASCVD, HFrEF, and CKD. In the same study, the multivariate analysis revealed that black ethnicity, female gender, and poor socio-economic status were associated with a lower utilization rate of SGLT2is.[106] Reportedly, only 32.9% of the eligible population with DKD at risk of disease progression received SGLT2i therapy in real-world clinical practice.[107]

Adoption of novel therapeutic agents are impacted by critical barriers that include decreased access to quality CKD care, lack of specialists familiar with the benefits of SGLT2i use, provider bias or pre-conceived notions of physicians that certain groups of patients may be less likely to adhere to treatment with an expensive agent, and prescription abandonment owing to socio-economic barriers.[106] Affordability and out-of-pocket costs of SGLT2is may be prohibitive resulting in prescription abandonment, especially since the cost of older therapies are more affordable.

Additionally, it is well established that overall, HTN, CVD, HF, and CKD co-morbidities each and collectively are more significant in racial/ethnic populations, and thus the potential benefits of SGLT2is may have a greater impact on cardio-renal disease in the black population.

Racial and ethnic variations in etiology, incidence, prevalence, disease burden, and response to treatment are well recognized with especially striking disparities between patients of African

ancestry and other racial populations.[108,109]Patients of African ancestry are known to harbour genetic traits that result in diminished response to key pharmacological therapies. This is further complicated by the lack of a robust assessment of the effect of treatments in black patients because of their under-representation in clinical trials. The under-representation of clinical trial participants with African descent in landmark clinical studies conducted worldwide on SGLTis are glaring. Trial participants of black or African ancestry accounted for approximately 5% of the total trial population (Table 2) .[110] Additionally, more than 99% of Black patients enrolled were from the Americas with considerable differences in the socioeconomic factors, health behavior, and access to health care compared to those living in the African continent.

9. Safety Outcomes with SGLT2i

While SGLT2is have an acceptable safety profile, some adverse events reported with their use include diabetic ketoacidosis (DKA), genital mycotic infection, UTI, risk of lower limb complications and volume depletion. SGLT2i agents induce glucosuric effects resulting from reduced reabsorption of glucose in kidney tubules, which may favor the growth of pathogenic microbes, thereby suggesting an increased risk of genital and urinary tract infections. In 2015, the FDA warned of a possible risk of severe UTI with the use of SGLT2i agents;[111] however, subsequent findings from population-based studies and meta-analysis revealed no significant association of SGLT2is with clinically significant UTI, compared with either placebo[112,113] or other glucose-lowering agents.[67,114–116] In the CREDENCE trial, the rate of UTI with canagliflozin was not significantly different from the placebo.[90] A meta-analysis of RCTs reported that SGLT2i use aggravated the risk of genital infections by 3-fold in patients with T2DM and CKD.[117] Genital infections occur more frequently among female users of SGLT2is and those with a prior history

of such infections.[118,119] Of note, such infectious complications resulting from SGLT2i use are generally mild and can be treated by antifungal medications, without necessitating discontinuation of treatment.[120]

Volume depletion is another concern among SGLT2i users resulting from its diuretic effects. For patients at risk of hypovolemia, decrease in the dose of thiazide or loop diuretics is recommended by the KDIGO2022 guidelines prior to initiation of SGLT2i treatment. [63,121]

In the CANVAS trial, allocation to SGLT2i therapy resulted in two-fold higher risk of lower limb amputation in comparison to a placebo (6.3 vs 3.4 events per 1000 patient-years respectively); however, analysis of other 12 trials revealed no statistically significant association between the use of SGLT2i and instances of lower limb amputation (relative risk [RR] of 1.06; 95% CI, 0.93 to 1.21).[122] A meta-analysis concluded that compared with non- SGLT2i users, the risks of amputation and PAD were slightly increased in patients with canagliflozin treatment.[123] Monitoring optimal body weight and blood pressure reduction is an important risk precaution action for patients at high risk of lower limb complications during the SGLT2i treatment course. Patients should be educated on examining their foot every day for cuts, redness, swelling, sores, blisters, corns, calluses and ensure appropriate hygiene.

Considering the hemodynamic effects of SGLT2is, their initiation may be associated with an initial slight decrease in eGFR, in the same way as RAAS blockers. However, initiation of SGLT2i does not require alteration in the frequency of CKD monitoring and the reversible decrease in eGFR does not require discontinuation of SGLT2i therapy.[124] In fact, the existence of this initial alteration is correlated with better subsequent nephroprotection.[125,126] Thus, monitoring of renal function beyond what is performed in general clinical practice is not required. Nevertheless, in

view of these data and the opinion of key experts, a reduction in eGFR levels by >30% warrants careful assessment of volume status and the temporary discontinuation of SGLT2i therapy.[125]

SGLT2i associated DKA, although rarely reported in T2DM patients, is usually accompanied by normal or mildly elevated blood glucose concentrations, which may remain unnoticed, leading to delayed diagnosis and potentially fatal consequences.[127] Both T1 and T2DM patients using insulin are at higher risk of ketoacidosis, particularly with T1DM and latent autoimmune diabetes in adults phenotype.[128] In the CREDENCE[83] and EMPA-KIDNEY[91] trials, the incidence of DKA events was relatively higher with SGLT2i treatment compared to placebo; however, the absolute rates were low, whereas DAPA-CKD reported no DKA cases with the use of dapagliflozin (compared to 2 cases with placebo).[90]

Further, the CANVAS trial identified a significant association between lower extremity amputation and bone fractures with the use of canagliflozin.[129] However, the CREDENCE trial reported a similar rate of amputation and fractures in patients with CKD treated with canagliflozin and placebo.[83] Likewise, the DAPA-CKD[90] and EMPA-KIDNEY[91] trials confirmed no increased risk of amputation or fractures with the use of dapagliflozin and empagliflozin, compared with placebo. Reassuringly, no increased risk of adverse events including AKI, hyperkalemia, and hypoglycemia were evident with the use of SGLT2is in patients with CKD.[83,90,91]

Before prescribing SGLT2is, patients should be well-informed of the potential adverse events and their signs and symptoms thereby facilitating early identification and appropriate management to prevent them from becoming a major barrier to their optimal utilization in the eligible population **[Table 3]**.[62,130,131]

10. Prescribing SGLT2i in Patients with CKD

The KDIGO 2022 clinical practice guidelines for T2DM management in CKD recommends a lower eGFR threshold of ≥20 ml/min per 1.73 m^2 for prescribing SGLT2is to improve clinical outcomes in patients with CKD and T2DM. Once initiated, SGLT2i therapy is recommended to be continued even at lower eGFR levels until the patient requires dialysis.[130] Further, glucagon-like peptide 1 receptor agonist is recommended in patients who do not meet their individualized glycemic target using metformin and/or SGLT2is or when the initiation of these drugs is not possible (for eGFR <20 ml/min/1.73 m^2).[130,132]

In view of cardioprotective outcomes exhibited by SGLT2i therapy, the UK Kidney Association guideline recommend their use in albuminuria patients with UACR ≥25 mg/mmol requiring modification of CV risk, with or without T2DM (with eGFR ≥25 ml/min/1.73 m^2).[131] Based on the recent EMPA-KIDNEY trial involving patients with CKD irrespective of their albuminuria status, updated recommendations may expand the indications for SGLT2i use to non-albuminuric patients as well.[91]

Based on the guideline recommendations for SGLT2i use in CKD management, the key experts have outlined a treatment algorithm to facilitate the safe implementation of SGLT2i therapy into clinical practice by primary care physicians **[Table 1 and Fig 5]**.

11. Recommendations from the African Association of Nephrology (AFRAN)

Based on the above discussion and the opinion of the experts, the key points related to the CKD burden, contributing risk factors, and barriers and challenges in ensuring optimum kidney care to patients with CKD have been summarized in **this manuscript**. Additionally, the experts have proposed recommendations on the use of SGLT2is in patients with CKD to guide nephrologists and primary care physicians in their decision-making **[Table 1]**.

A few key limitations of this manuscript are the lack of adapting published international guidelines such as the KDIGO into the regional context through the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument that would enable addressing barriers and challenges associated with identification, management, and use of evidence-based medications in CKD.

Similarly, grading of evidence was not performed as a part of this manuscript's development and future systematic reviews in the African region on the efficacy and safety of SGLT2is should be envisaged.

12. Conclusion

The substantial burden of CKD in Africa highlights the need for a concerted effort towards the development of effective prevention and mitigation strategies to overcome the high health and economic burden that this condition entails in a region that has significant resource constraints. There are several barriers to optimal CKD screening, early detection, and timely intervention to delay the progression to KF. SGLT2is have emerged as a potent therapeutic agent with mounting evidence of cardiorenal protective effects with broad indications in T2DM, CKD, and CV diseases. SGLT2is play a significant role in CKD management especially in delaying progression to KF in patients who have albuminuria with or without T2DM. However, further research to evaluate their safety and effectiveness in African patients is warranted to further establish these effects in a population that is ethnically and socioeconomically diverse.

Similarly, there is an imminent need for a multidisciplinary consensus guidelines involving other members in the CKD care management system such as primary care physicians, social workers, lateral specializations, nutritionists, pharmacists, and community leaders, to be developed in the African region.

Acknowledgments

The authors would like to acknowledge Parul Rishi and Dr. Sushma Jayan, of Fortrea Scientific Pvt. Ltd. (formerly Labcorp Scientific Services & Solutions Pvt. Ltd.) for medical writing support which was done in accordance with Good Publication Practices 2022 guidelines.

Funding

Medical writing assistance for this manuscript is funded by AstraZeneca International.

Disclosures

FJ has received a speaker honorarium from Servier and AstraZeneca; travel support for meetings from Servier, Pfizer, and AstraZeneca. IIU has received research support from International Diabetes Federation and Sanofi Pasteur; speaker honorarium from AstraZeneca and Boehringer Ingelheim. SN has received research support from Newton Fund via Medical Research Council (MRC) (United Kingdom) and MRC (South Africa). HB has received speaker honorarium from Novartis, Boehringer Ingelheim, Sanofi, and AstraZeneca. DIMW has received speaker honorarium from Pfizer and served as President for Renal Association (of Mauritius). AN, EKT, EKS, MYC, YTM, FFK, MHH, and KHY declared no competing interests.

13. References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Int J Nephrol. January 2013;3(1). https://kdigo.org/wpcontent/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed November 1, 2022

2. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2020;395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3

3. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed July 3, 2023.

4. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2019;34(11):1803-1805. doi:10.1093/ndt/gfz174

5. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet Lond Engl*. 2013;382(9888):260-272. doi:10.1016/S0140-6736(13)60687-X

6. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease. *Circulation*. 2021;143(11):1157-1172. doi:10.1161/CIRCULATIONAHA.120.050686

7. Cozzolino M, Mangano M, Stucchi A, et al. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018 Oct 1;33(suppl_3):iii28-iii34. doi:10.1093/ndt/gfy174

8. Sarnak MJ, Amann K, Bangalore S, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74(14):1823-1838. doi:10.1016/j.jacc.2019.08.1017

9. Provenzano M, Coppolino G, De Nicola L, et al. Unraveling Cardiovascular Risk in Renal Patients: A New Take on Old Tale. *Front Cell Dev Biol*. 2019;7. https://www.frontiersin.org/articles/10.3389/fcell.2019.00314. Accessed December 23, 2022.

10. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9

11. El Nahas M, Barsoum R, Dirks JH, Remuzzi G, eds. Kidney Diseases in the Developing World and Ethnic Minorities. Routledge & CRC Press; 2005

12. Ogundele SB. Chronic kidney disease in Sub-Saharan Africa. *Saudi J Kidney Dis Transplant*. 2018;29(5):1188. doi:10.4103/1319-2442.243945

13. Etheredge H, Paget G. Ethics and Rationing Access to Dialysis in Resource-Limited Settings: The Consequences of Refusing a Renal Transplant in the South African State Sector. *Dev World Bioeth*. 2015;15(3):233-240. doi:10.1111/dewb.12067

14. Arnold SV, Tang F, Cooper A, et al. Global use of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. Results from DISCOVER. *BMC Endocr Disord*. 2022;22:111. doi:10.1186/s12902-022-01026-2

15. Jarraya F. Chronic Kidney Disease: Global Burden and Perspectives for Africa. In: Modesti P, Cappuccio F, Parati G, eds. Ethnic Diversities, Hypertension and Global Cardiovascular Risk. Updates in Hypertension and Cardiovascular Protection. Springer. https://www.springer.com/series/15049. Accessed February 15, 2023. https://doi.org/10.1007/978-3-319-93148-7_9

16. Stanifer JW, Jing B, Tolan S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(3):e174-181. doi:10.1016/S2214-109X(14)70002-6

17. Oguejiofor F, Kiggundu DS, Bello AK, et al. International Society of Nephrology Global Kidney Health Atlas: structures, organization, and services for the management of kidney failure in Africa. *Kidney Int Suppl*. 2021;11(2):e11-e23. doi:10.1016/j.kisu.2021.01.009

18. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. *BMC Nephrol*. 2018;19(1):125. doi:10.1186/s12882-018-0930-5

19. Oluyombo R, Banjo Oguntade H, Soje M, Obajolowo O, Karim M. Obesity and CKD in Sub-Saharan Africa: A Narrative Review. *Kidney Med*. 2022;4(2):100403. doi:10.1016/j.xkme.2021.11.001

20. Abd ElHafeez S, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. *BMJ Open*. 2018;8(1):e015069. doi:10.1136/bmjopen-2016-015069

21. Ajayi SO, Ekrikpo UE, Ekanem AM, et al. Prevalence of Chronic Kidney Disease as a Marker of Hypertension Target Organ Damage in Africa: A Systematic Review and Meta-Analysis. *Int J Hypertens*. 2021;2021:e7243523. doi:10.1155/2021/7243523

22. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol JASN*. 2011;22(11):2129-2137. doi:10.1681/ASN.2011040388

23. Mansour M, Djenaba B, Ahmed LT, Moustapha CM, Abdou N. Chronic Kidney Disease in Sub-Saharan Africans: A Study of 462 Patients. *Open J Nephrol*. 2021;11(1):114-122. doi:10.4236/ojneph.2021.111009

24. Ulasi II, Ijoma CK. The Enormity of Chronic Kidney Disease in Nigeria: The Situation in a Teaching Hospital in South-East Nigeria. *J Trop Med*. 2010;2010:e501957. doi:10.1155/2010/501957

25. De Broe ME, Gharbi MB, Elseviers M. Maremar, prevalence of chronic kidney disease, how to avoid over-diagnosis and under-diagnosis. *Nephrol Ther*. 2016;12 Suppl 1:S57-63. doi:10.1016/j.nephro.2016.02.013

26. Muiru AN, Charlebois ED, Balzer LB, et al. The epidemiology of chronic kidney disease (CKD) in rural East Africa: A population-based study. *PLoS ONE*. 2020;15(3):e0229649. doi:10.1371/journal.pone.0229649

27. Fabian J, Kalyesubula R, Mkandawire J, et al. Measurement of kidney function in Malawi, South Africa, and Uganda: a multicentre cohort study. *Lancet Glob Health*. 2022;10(8):e1159-e1169. doi:10.1016/S2214-109X(22)00239-X

28. Ashuntantang G, Osafo C, Olowu WA, et al. Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. *Lancet Glob Health*. 2017;5(4):e408-e417. doi:10.1016/S2214-109X(17)30057-8

29. Katz IJ, Gerntholtz T, Naicker S. Africa and Nephrology: The Forgotten Continent. *Nephron Clin Pract*. 2011;117(4):320-327. doi:10.1159/000321524

30. Peralta CA, Risch N, Lin F, et al. The Association of African Ancestry and elevated creatinine in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Nephrol*. 2010;31(3):202-208. doi:10.1159/000268955

31. Peralta CA, Vittinghoff E, Bansal N, et al. Trajectories of Kidney Function Decline in Young Black and White Adults With Preserved GFR: Results From the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis*. 2013;62(2):261-266. doi:10.1053/j.ajkd.2013.01.012

32. Kasembeli AN, Duarte R, Ramsay M, Naicker S. African origins and chronic kidney disease susceptibility in the human immunodeficiency virus era. *World J Nephrol*. 2015;4(2):295-306. doi:10.5527/wjn.v4.i2.295

33. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-based Studies from 90 Countries. *Circulation*. 2016;134(6):441-450. doi:10.1161/CIRCULATIONAHA.115.018912

34. Sun Y, Zhang J ning, Zhao D, et al. Role of the epithelial sodium channel in salt-sensitive hypertension. *Acta Pharmacol Sin*. 2011;32(6):789-797. doi:10.1038/aps.2011.72

35. Chen TK, Katz R, Estrella MM, et al. Association of APOL1 Genotypes With Measures of Microvascular and Endothelial Function, and Blood Pressure in MESA. J Am Heart Assoc. 2020 Sep;9(17):e017039. doi: 10.1161/JAHA.120.017039Accessed December 9, 2022

36. Luyckx VA, Perico N, Somaschini M, et al. A Developmental Approach to the Prevention of Hypertension and Kidney Disease – a report from the Birth Weight and Nephron Number Working Group. *Lancet Lond Engl*. 2017;390(10092):424-428. doi:10.1016/S0140-6736(17)30576-7

37. Jikamo B, Adefris M, Azale T, Alemu K. Incidence, trends and risk factors of preeclampsia in sub-Saharan Africa: a systematic review and meta-analysis. *PAMJ - One Health*. 2023;11(1). doi:10.11604/pamj-oh.2023.11.1.39297

38. Zhai R, Liu Y, Tong J, et al. Empagliflozin Ameliorates Preeclampsia and Reduces Postpartum Susceptibility to Adriamycin in a Mouse Model Induced by Angiotensin Receptor Agonistic Autoantibodies. *Front Pharmacol*. 2022;13:826792. doi:10.3389/fphar.2022.826792

39. ElHafeez SA, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. *BMJ Open*. 2018;8(1):e015069. doi:10.1136/bmjopen-2016-015069

40. Okyere P, Okyere I, Ephraim RKD, et al. Spectrum and Clinical Characteristics of Renal Diseases in Ghanaian Adults: A 13-Year Retrospective Study. *Int J Nephrol*. 2020;2020:8967258. doi:10.1155/2020/8967258

41. International Diabetes Foundation. Diabetes in Africa. https://www.idf.org/ournetwork/regions-members/africa/diabetes-in-africa.html. Accessed December 9, 2022

42. Sumaili EK, Cohen EP, Zinga CV, Krzesinski JM, Pakasa NM, Nseka NM. High prevalence of undiagnosed chronic kidney disease among at-risk population in Kinshasa, the Democratic Republic of Congo. *BMC Nephrol*. 2009;10(1):18. doi:10.1186/1471-2369-10-18

43. Okpechi IG, Ameh OI, Bello AK, Ronco P, Swanepoel CR, Kengne AP. Epidemiology of Histologically Proven Glomerulonephritis in Africa: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2016;11(3):e0152203. doi:10.1371/journal.pone.0152203

44. Hodel NC, Hamad A, Praehauser C, et al. The epidemiology of chronic kidney disease and the association with non-communicable and communicable disorders in a population of sub-Saharan Africa. *PLOS ONE*. 2018;13(10):e0205326. doi:10.1371/journal.pone.0205326

45. Ayokunle DS, Olusegun OT, Ademola A, Adindu C, Olaitan RM, Oladimeji AA. Prevalence of chronic kidney disease in newly diagnosed patients with Human

immunodeficiency virus in Ilorin, Nigeria. *J Bras Nefrol Orgao Of Soc Bras E Lat-Am Nefrol*. 2015;37(2):177-184. doi:10.5935/0101-2800.20150029

46. Anyabolu EN, Chukwuonye II, Arodiwe E, Ijoma CK, Ulasi I. Prevalence and predictors of chronic kidney disease in newly diagnosed human immunodeficiency virus patients in Owerri, Nigeria. *Indian J Nephrol*. 2016;26(1):10-15. doi:10.4103/0971-4065.156115

47. Agaba EI, Agaba PA, Sirisena ND, Anteyi EA, Idoko JA. Renal disease in the acquired immunodeficiency syndrome in north central Nigeria. *Niger J Med J Natl Assoc Resid Dr Niger*. 2003;12(3):120-125.

48. Ekrikpo UE, Kengne AP, Akpan EE, et al. Prevalence and correlates of chronic kidney disease (CKD) among ART-naive HIV patients in the Niger-Delta region of Nigeria. *Medicine (Baltimore)*. 2018;97(16):e0380. doi:10.1097/MD.0000000000010380

49. Ekrikpo UE, Kengne AP, Bello AK, et al. Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PloS One*. 2018;13(4):e0195443. doi:10.1371/journal.pone.0195443

50. Booth JW, Hamzah L, Jose S, et al. Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2016;31(12):2099-2107. doi:10.1093/ndt/gfv436

51. Foy MC, Estrella MM, Lucas GM, et al. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. *Clin J Am Soc Nephrol CJASN*. 2013;8(9):1524-1532. doi:10.2215/CJN.10991012

52. Post FA, Campbell LJ, Hamzah L, et al. Predictors of renal outcome in HIV-associated nephropathy. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008;46(8):1282-1289. doi:10.1086/529385

53. Kiire CF. Hepatitis B infection in sub-Saharan Africa. *Vaccine*. 1990;8:S107-S112. doi:10.1016/0264-410X(90)90229-F

54. Spearman CW, Afihene M, Ally R, et al. Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. *Lancet Gastroenterol Hepatol*. 2017;2(12):900-909. doi:10.1016/S2468-1253(17)30295-9

55. Ogunleye A, Oluwafemi TT, Akinbodewa AA, Daomi VO, Adejumo OA, Omisakin TC. Seroprevalence of Hepatitis B, C and coinfection among patients with chronic kidney disease in a Nigerian hospital. *Saudi J Kidney Dis Transplant*. 2020;31(3):647. doi:10.4103/1319-2442.289451

56. Prasad N, Patel MR. Infection-Induced Kidney Diseases. *Front Med*. 2018;5. https://www.frontiersin.org/articles/10.3389/fmed.2018.00327. Accessed December 10, 2022.

57. Shlipak MG, Tummalapalli SL, Boulware LE, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2021;99(1):34-47. doi:10.1016/j.kint.2020.10.012

58. Cheung AK, Chang TI, Cushman WC, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int*. 2021;99(3):S1-S87. doi:10.1016/j.kint.2020.11.003

59. Brenner BM, Mitch WE, Zhang Z. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2001:9.

60. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. *N Engl J Med*. 2001;345(12):851-860. doi:10.1056/NEJMoa011303

61. Chao EC, Henry RR. SGLT2 inhibition — a novel strategy for diabetes treatment. *Nat Rev Drug Discov*. 2010;9(7):551-559. doi:10.1038/nrd3180

62. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. *Kidney Int Rep*. 2022;7(7):1463-1476. doi:10.1016/j.ekir.2022.04.094

63. Rossing P, Caramori ML, Chan JCN, et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2022;102(5):S1-S127. doi:10.1016/j.kint.2022.06.008

64. Cherney DZI, Dagogo-Jack S, McGuire DK, et al. Kidney outcomes using a sustained ≥40% decline in eGFR: A meta-analysis of SGLT2 inhibitor trials. *Clin Cardiol*. 2021;44(8):1139-1143. doi:10.1002/clc.23665

65. Nagasu H, Yano Y, Kanegae H, et al. Kidney Outcomes Associated With SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs in Real-world Clinical Practice: The Japan Chronic Kidney Disease Database. *Diabetes Care*. 2021;44(11):2542-2551. doi:10.2337/dc21-1081

66. Khunti K, Kosiborod M, Kim DJ, et al. Cardiovascular outcomes with sodium–glucose cotransporter-2 inhibitors vs other glucose-lowering drugs in 13 countries across three continents: analysis of CVD-REAL data. *Cardiovasc Diabetol*. 2021;20(1):159. doi:10.1186/s12933-021-01345-z

67. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020;8(1):27-35. doi:10.1016/S2213-8587(19)30384-5

68. Fadini GP, Solini A, Manca ML, et al. Effectiveness of dapagliflozin versus comparators on renal endpoints in the real world: A multicentre retrospective study. *Diabetes Obes Metab*. 2019;21(2):252-260. doi:10.1111/dom.13508

69. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. *Kidney Int Rep*. 2022;7(7):1463-1476. doi:10.1016/j.ekir.2022.04.094

70. Meraz-Muñoz AY, Weinstein J, Wald R. eGFR Decline after SGLT2 Inhibitor Initiation: The Tortoise and the Hare Reimagined. *Kidney360*. 2021;2(6):1042-1047. doi:10.34067/KID.0001172021

71. Liu AYL, Low S, Yeoh E, et al. A real-world study on SGLT2 inhibitors and diabetic kidney disease progression. *Clin Kidney J*. 2022;15(7):1403-1414. doi:10.1093/ckj/sfac044

72. McEwan P, Boyce R, Sanchez JJG, et al. Extrapolated longer-term effects of the DAPA-CKD trial: a modelling analysis. *Nephrol Dial Transplant*. 2022;38(5):1260-1270. doi:10.1093/ndt/gfac280

73. EMPA-KIDNEY Collaborative Group. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2022;37(7):1317-1329. doi:10.1093/ndt/gfac040

74. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J*. 2018;11(6):749-761. doi:10.1093/ckj/sfy090

75. Heerspink HJL, Vart P, Jongs N, et al. Estimated lifetime benefit of novel pharmacological therapies in patients with type 2 diabetes and chronic kidney disease: A joint analysis of randomized controlled clinical trials. *Diabetes Obes Metab*. 2023;25(11):3327-3336. doi:10.1111/dom.15232

76. Feldman HI, Appel LJ, Chertow GM, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. *J Am Soc Nephrol JASN*. 2003;14(7 Suppl 2):S148-153. doi:10.1097/01.asn.0000070149.78399.ce

77. Expanding access to newer medicines for people with type 2 diabetes in low-income and middle-income countries: a cost-effectiveness and price target analysis. *Lancet Diabetes Endocrinol*. 2021;9(12):825-836. doi:10.1016/S2213-8587(21)00240-0

78. McEwan P, Darlington O, Miller R, et al. Cost-Effectiveness of Dapagliflozin as a Treatment for Chronic Kidney Disease: A Health-Economic Analysis of DAPA-CKD. *Clin J Am Soc Nephrol CJASN*. 2022;17(12):1730-1741. doi:10.2215/CJN.03790322

79. Tirucherai GS, LaCreta F, Ismat FA, Tang W, Boulton DW. Pharmacokinetics and pharmacodynamics of dapagliflozin in children and adolescents with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2016;18(7):678-684. doi:10.1111/dom.12638

80. Laffel LM, Danne T, Klingensmith GJ, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol*. 2023;11(3):169-181. doi:10.1016/S2213-8587(22)00387-4

81. Liu J, Cui J, Fang X, et al. Efficacy and Safety of Dapagliflozin in Children With Inherited Proteinuric Kidney Disease: A Pilot Study. *Kidney Int Rep*. 2021;7(3):638-641. doi:10.1016/j.ekir.2021.12.019

82. Grube PM, Beckett RD. Clinical studies of dapagliflozin in pediatric patients: a rapid review. *Ann Pediatr Endocrinol Metab*. 2022;27(4):265-272. doi:10.6065/apem.2244166.083

83. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744

84. Heerspink HJL, Jongs N, Chertow GM, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(11):743-754. doi:10.1016/S2213-8587(21)00242-4

85. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038

86. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

87. Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia*. 2021;64(6):1256-1267. doi:10.1007/s00125-021-05407-5

88. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. *Diabet Med*. 2010;27(2):136-142. doi:10.1111/j.1464-5491.2009.02894.x

89. Zhao JZ, Weinhandl ED, Carlson AM, St. Peter WL. Hypoglycemia Risk With SGLT2 Inhibitors or Glucagon-Like Peptide 1 Receptor Agonists Versus Sulfonylureas Among Medicare Insured Adults With CKD in the United States. *Kidney Med*. 2022;4(8):100510. doi:10.1016/j.xkme.2022.100510

90. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816

91. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

92. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int*. 2018;93(1):231-244. doi:10.1016/j.kint.2017.06.017

93. Oktaviono YH, Kusumawardhani N. Hyperkalemia Associated with Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blockers in Chronic Kidney Disease. *Acta Medica Indones*. 2020;52(1):74-79.

94. Neuen BL, Oshima M, Perkovic V, et al. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. *Eur Heart J*. 2021;42(48):4891-4901. doi:10.1093/eurheartj/ehab497

95. Neuen BL, Oshima M, Agarwal R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. *Circulation*. 2022;145(19):1460-1470. doi:10.1161/CIRCULATIONAHA.121.057736

96. Weir MR, Slee A, Sun T, et al. Effects of canagliflozin on serum potassium in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

97. Chertow GM, Vart P, Jongs N, et al. Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. *J Am Soc Nephrol*. 2021;32(9):2352-2361. doi:10.1681/ASN.2021020167

98. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190

99. Wheeler DC, Toto RD, Stefánsson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. 2021;100(1):215-224. doi:10.1016/j.kint.2021.03.033

100. Heerspink HJL, Cherney D, Postmus D, et al. A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function. *Kidney Int*. 2022;101(1):174-184. doi:10.1016/j.kint.2021.09.005

101. Wheeler DC, Jongs N, Stefansson BV, et al. Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial. *Nephrol Dial Transplant*. 2022;37(9):1647-1656. doi:10.1093/ndt/gfab335

102. Ujjawal A, Schreiber B, Verma A. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) in kidney transplant recipients: what is the evidence? *Ther Adv Endocrinol Metab*. 2022;13:20420188221090000. doi:10.1177/20420188221090001

103. Lim JH, Kwon S, Jeon Y, et al. The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients. *Transplantation*. 2022;106(9):e404. doi:10.1097/TP.0000000000004228

104. Committee on Quality of Health Care in America. Crossing the Quality Chasm: (317382004-001). doi:10.1037/e317382004-001

105. Nishi L, Ghossein C, Srivastava A. Increasing Sodium-Glucose Cotransporter 2 Inhibitor Use in CKD: Perspectives and Presentation of a Clinical Pathway. *Kidney Med*. 2022;4(5):100446. doi:10.1016/j.xkme.2022.100446

106. Eberly LA, Yang L, Eneanya ND, et al. Association of Race/Ethnicity, Gender, and Socioeconomic Status With Sodium-Glucose Cotransporter 2 Inhibitor Use Among Patients With Diabetes in the US. *JAMA Netw Open*. 2021;4(4):e216139. doi:10.1001/jamanetworkopen.2021.6139

107. Jeong SJ, Lee SE, Shin DH, Park IB, Lee HS, Kim KA. Barriers to initiating SGLT2 inhibitors in diabetic kidney disease: a real-world study. *BMC Nephrol*. 2021;22(1):177. doi:10.1186/s12882-021-02381-3

108. Kf D, Mo O, Is A, et al. Efficacy of Dapagliflozin in Black Versus White Patients With Heart Failure and Reduced Ejection Fraction. *JACC Heart Fail*. 2022;10(1). doi:10.1016/j.jchf.2021.08.006

109. Nasser SA, Arora N, Ferdinand KC. Addressing Cardiovascular Disparities in Racial/Ethnic Populations: The Blood Pressure-Lowering Effects of SGLT2 Inhibitors. *Rev Cardiovasc Med*. 2022;23(12):411. doi:10.31083/j.rcm2312411

110. Clemmer JS, Ward TJ, Lirette ST. Retrospective analysis of SGLT2 inhibitors in heart failure with preserved ejection fraction. *ESC Heart Fail*. 2023;10(3):2010-2018. doi:10.1002/ehf2.14347

111. Research C for DE and. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. *FDA*. March 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious. Accessed December 20, 2022

112. Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2018;55(5):503-514. doi:10.1007/s00592-018-1116-0

113. Liu J, Li L, Li S, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep*. 2017;7:2824. doi:10.1038/s41598-017-02733-w

114. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744

115. Donnan JR, Grandy CA, Chibrikov E, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. *BMJ Open*. 2019;9(1):e022577. doi:10.1136/bmjopen-2018-022577

116. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med*. 2019;171(4):248. doi:10.7326/M18-3136

117. Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2019;21(5):1237-1250. doi:10.1111/dom.13648

118. Thong KY, Yadagiri M, Barnes DJ, et al. Clinical risk factors predicting genital fungal infections with sodium–glucose cotransporter 2 inhibitor treatment: The ABCD nationwide dapagliflozin audit. *Prim Care Diabetes*. 2018;12(1):45-50. doi:10.1016/j.pcd.2017.06.004

119. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):323-334. doi:10.1056/NEJMoa1515920

120. Engelhardt K, Ferguson M, Rosselli JL. Prevention and Management of Genital Mycotic Infections in the Setting of Sodium-Glucose Cotransporter 2 Inhibitors. *Ann Pharmacother*. 2021;55(4):543-548. doi:10.1177/1060028020951928

121. Tuttle KR, Brosius FC, Cavender MA, et al. SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. *Diabetes*. 2021;70(1):1-16. doi:10.2337/dbi20-0040

122. Baigent C, Emberson J, Haynes R, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *The Lancet*. 2022;400(10365):1788-1801. doi:10.1016/S0140-6736(22)02074-8

123. Lin C, Zhu X, Cai X, et al. SGLT2 inhibitors and lower limb complications: an updated meta-analysis. *Cardiovasc Diabetol*. 2021;20(1):91. doi:10.1186/s12933-021-01276-9

124. KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2023. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2023-CKD-Guideline-Public-Review-Draft_5-July-2023.pdf. Accessed November 17, 2023

125. Heerspink HJL, Cherney DZI. Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation. *Clin J Am Soc Nephrol CJASN*. 2021;16(8):1278-1280. doi:10.2215/CJN.02480221

126. Jongs N, Chertow GM, Greene T, et al. Correlates and Consequences of an Acute Change in eGFR in Response to the SGLT2 Inhibitor Dapagliflozin in Patients with CKD. *J Am Soc Nephrol*. 2022;33(11):2094. doi:10.1681/ASN.2022030306

127. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. *World J Diabetes*. 2021;12(5):514-523. doi:10.4239/wjd.v12.i5.514

128. Buzzetti R, Tuomi T, Mauricio D, et al. Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel. *Diabetes*. 2020;69(10):2037-2047. doi:10.2337/dbi20-0017

129. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

130. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2022;102(5):974-989. doi:10.1016/j.kint.2022.08.012

131. UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease. Accessed December 23, 2022

132. Alicic R, Nicholas SB. Diabetic Kidney Disease Back in Focus: Management Field Guide for Health Care Professionals in the 21st Century. *Mayo Clin Proc*. 2022;97(10):1904-1919. doi:10.1016/j.mayocp.2022.05.003

133. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617. doi:10.1016/S2213-8587(19)30180-9

134. Cahn A, Raz I, Leiter LA, et al. Cardiovascular, Renal, and Metabolic Outcomes of Dapagliflozin Versus Placebo in a Primary Cardiovascular Prevention Cohort: Analyses From DECLARE-TIMI 58. *Diabetes Care*. 2021;44(5):1159-1167. doi:10.2337/dc20-2492

135. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med*. 2020;383(15):1425-1435. doi:10.1056/NEJMoa2004967

136. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2021;384(2):129-139. doi:10.1056/NEJMoa2030186

1 **Tables:**

2 **Table 1: Recommendations for prescribing SGLT2i therapy in CKD**

Indications
• Congestive heart failure (eGFR >20 ml/min per 1.73 m^2) • Established ASCVD or high risk for ASCVD in patients with T2DM (eGFR ≥30 ml/min per 1.73 m^2) • CKD with or without T2DM*, with eGFR ≥20ml/min/1.73m2 and UACR ≥200mg/g • As an additional therapy with ACEi/ARBs at maximum tolerated dose of SGLT2i • To be prescribed in the earlier CKD stages to improve clinical outcomes.
Uncertain indications
• T1DM • eGFR <20ml/min/1.73m^2 (maybe continued till patient requires dialysis) • Insufficient evidence of use in polycystic kidney disease, lupus nephritis, vasculitides, and type 1 DKD • No clear evidence for discontinuation during AKI unless contraindicated based on concerns about efficacy or the pill count. In that case, treatment should be resumed at the earliest.**
Key practice points: • Since there is no evidence of a graded dose response, titrating to a higher dose is not necessary for maximizing the cardiorenal benefits. Notably, while a higher dose of SGLT2i may improve glycemic control, the glucose-lowering effect of SGLT2i decreases at lower eGFR levels. • SGLT2i should be initiated at the lowest recommended daily dose: canagliflozin 100 mg, dapagliflozin 10 mg, empagliflozin 10 mg, or ertugliflozin 5 mg. • SGLT2is can be safely used in patients with CKD stages 1 to 4. • Initiation of SGLT2i therapy may lead to reversible decline in the eGFR and is generally not an indication to discontinue treatment. • No need for monitoring of renal function parameters and electrolytes at 1 month after initiating SGLT2i beyond what is performed in general clinical practice for patients with eGFR ≥20 to <45 ml/min/1.73m^2, UACR <200 mg/g, heart failure, and risk of volume depletion with concomitant use of RAAS blockers and loop diuretics.

- Consult diabetologist if there is confusion on the etiology of diabetes (T1DM, LADA, secondary diabetes due to pancreatitis) or if patient is taking multiple insulin injections or presenting significant glycemic imbalance (HbA1c >9%)
- No consultation needed if the patient is only treated with drugs that do not induce hypoglycemia (metformin, DPP-4i, GLP-1 RA) or no significant alteration of glycemic control is required.
- If the patient is already being treated with drugs inducing hypoglycemia (SU, glinides, insulin), it is necessary to consult diabetologist for adjustment of doses of these drugs.
- SGLT2i reduce HbA1c levels by a mean of 0.7% in patients with eGFR >60 ml/min/1.73 m^2.
- Physicians must check HbA1c levels before prescribing SGLT2i:
    - If HbA1c >8%, dose reduction of hypoglycemic drugs usually not necessary
    - If HbA1c is 7% to 8%, reduce the dose of SU or glinide by 50% and insulin dose by 10%; self-monitoring of blood glucose.
- If HbA1c <7%, SU or glinide can be discontinued and insulin dose reduction by 20%, self-monitoring of blood glucose. Initiation of SGLT2is is associated with a reduced risk of AKI in comparison to initiation of other anti-glycemic agents.***
- In case of non-diabetic patients detecting glucosuria is a simple parameter to assess therapy adherence when urine dipstick is available, due to resource constraints in many African countries, this may not be sustainable in the long term. Furthermore, a reduced renal threshold for glycosuria in some patients may negate this.

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; DKD, diabetic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; LADA, late onset diabetes of adulthood; RAAS, renin-angiotensin aldosterone system; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylureas; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio

*Non-diabetic kidney disease includes ischemic nephropathy, IgA nephropathy, FSGS, chronic pyelonephritis, chronic interstitial nephritis

**Carriazo S, Ortiz A. Stopping kidney protection in the elderly following acute kidney injury: think mortality. Clinical Kidney Journal. 2022 Jun;15(6):1037; Meraz-Muñoz AY, Weinstein J, Wald R. eGFR Decline after SGLT2 Inhibitor Initiation: The Tortoise and the Hare Reimagined. Kidney360. 2021 Jun 24;2(6):1042–7.

*** Zhuo M, Paik JM, Wexler DJ, Bonventre JV, Kim SC, Patorno E. SGLT2 Inhibitors and the Risk of Acute Kidney Injury in Older Adults with Type 2 Diabetes. Am J Kidney Dis. 2022 Jun;79(6):858-867.e1. doi: 10.1053/j.ajkd.2021.09.015

Table 2: Cardiovascular and kidney outcomes with SGLT2is in pivotal randomized clinical trials

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
EMPA-REG OUTCOME (2015, **2016)**[86,119] **(NCT01131676)**	HbA1c level: 7.0 to 9.0% Established CV disease eGFR: ≥30 ml/min/1.73 m^2	7 020	Small sample size reported as limitation of the study	Empagliflozin (1:1:1) (either 10 mg or 25 mg or placebo once daily)	3.1	CV death, MI, stroke HR, 0.86; 95.02% CI, (0.74–0.99); *P* = 0.04 (for superiority)	Worsening of nephropathy	Empagliflozin vs placebo 12.7% vs 18.8%; HR, 0.61; 95% CI, (0.53–0.70); *P* < 0.001
						Hospitalization for HF HR, 0.65; 95% CI, (0.50–0.85); *P* = 0.002	Doubling of the serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	1.5% vs 2.6%; HR, 0.56; 95% CI, (0.39–0.79); *P* < 0.001
							Initiation of KRT	0.3% vs 0.6%; HR, 0.45; 95% CI, (0.21–0.97); *P* = 0.04
							Progression to A3 albuminuria	11.2% vs 16.2%; HR, 0.62; 95% CI, (0.54–0.72); *P* < 0.001
							Rate of incident albuminuria (in patients with normal albumin at baseline)	51.5% vs 51.2%; HR, 0.95; 95% CI, (0.87–1.04); *P* = 0.25
							Death from kidney cause	Empagliflozin: 0.1%

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
CANVAS and CANVAS-R (2017)[129] (CANVAS: NCT01032629 ; CANVAS-R: NCT01989754)	T2DM 30 years or older with a prior history of symptomatic ASCVD or 50 years or older with at least 2 CV risk factors eGFR ≥30 ml/min/1.73 m^2	10 142 (CANVAS: 4 330, CANVAS-R: 5 812)	176 (3)	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	2.4	CV death, MI, stroke Canagliflozin vs placebo 26.9 vs. 31.5 participants per 1000 patient-years HR, 0.86; 95% CI, (0.75–0.97); $P < 0.001$ (for non-inferiority); $P = 0.02$ (for superiority) Hospitalization for HF 5.5 vs 8.7; HR, 0.67; 95% CI, (0.52–0.87)	Progression of albuminuria (participants per 1000 patient-years) Regression of albuminuria (participants per 1000 patient-years) Progression to A3 albuminuria (participants per 1000 patient-years)	89.4 vs. 128.7 HR, 0.73; 95% CI, (0.67–0.79) 293.4 vs. 187.5; HR, 1.70; 95% CI, (1.51–1.91) 89.4 vs 128.7; HR, 0.73; 95% CI (0.67–0.79)

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
							Composite outcome of sustained 40% reduction in eGFR, need for KRT, or death from kidney causes (participants per 1000 patient-years)	5.5 vs 9.0; HR, 0.60; 95% CI (0.47–0.77)
CREDENCE (2019)[83] **(NCT02065791)**	T2DM patients with CKD eGFR: 30 to <90 ml/min/1.73 m^2 UACR >300 to 5000 mg/g HbA1c level: 6.5% to 12.0%	4 401	112 (5.1)	Canagliflozin 100 mg once daily vs placebo	2.62	CV death, MI, stroke HR, 0.80; 95% CI, (0.67–0.95); *P* = 0.01	Relative risk of composite of KF, a doubling of the serum creatinine, or death from kidney or CV causes (participants per 1000 patient-years)	43.2 vs. 61.2 HR, 0.70; 95% CI, (0.59–0.82); *P* = 0.00001
						Hospitalization for HF HR, 0.61; 95% CI, (0.47–0.80); *P* < 0.001	Kidney-specific composite of KF, a doubling of the serum creatinine level, or death from kidney causes	HR, 0.66; 95% CI, (0.53–0.81); *P* < 0.001
							Relative risk of KF	HR, 0.68; 95% CI, (0.54–0.86); *P* = 0.002

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
EMPEROR-Reduced (2020)[98] (NCT03057977)	Chronic HFrEF	3 730	123 (6.6)	Empagliflozin 10 mg once daily vs placebo	1.3	CV death or hospitalization for HF 19.4% vs 24.7% (empagliflozin vs placebo) HR, 0.75; 95% CI, (0.65–0.86); *P* < 0.001	Annual rate of decline in eGFR	Empagliflozin vs placebo -0.55 vs. -2.28 ml/min/1.73 m^2; *P* < 0.001
DAPA-CKD (2020)[90] (NCT03036150)	Patients of CKD with or without T2DM eGFR: 25 to 75 ml/min/1.73 m^2 UACR: 200 to 5000 mg/g	4 304	104 (4.8)	Dapagliflozin 10 mg vs placebo once daily	2.4	CV death or hospitalization for HF HR, 0.71; 95% CI, (0.55–0.92); *P* = 0.009	Occurrence of the composite of a sustained decline in the eGFR of at least 50%, KF, or death from kidney or CV related causes Risk of composite of a sustained decline in the eGFR of at least 50%, KF, or death from kidney-related causes	Dapagliflozin vs. placebo 9.2% vs 14.5%; HR, 0.61; 95% CI, (0.51–0.72); *P* < 0.001 HR, 0.56; 95% CI, (0.45–0.68); *P* < 0.001
DECLARE-TIMI 58 (2019, **2021)[133,134]**	Patients with T2DM	17 160	Not mentioned	Dapagliflozin 10 mg once daily vs	4.2	CV death or hospitalization for HF (among	Cardiorenal composite outcome	HR, 0.76: 95% CI, (0.67 to 0.87); *P* < 0.0001

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
(NCT01730534)	Established ASCVD or multiple risk factors for ASCVD HbA1c level: (6.5% to 12.0%) Creatinine clearance of ≥60 ml/min			matched placebo (1:1)		patients with multiple risk factors) HR, 0.84, 95% CI, (0.67–1.04)	Kidney-specific outcome KF or death from kidney causes Sustained decline in eGFR by at least 40% to less than 60 ml/min/ 1.73 m^2 eGFR UACR	HR, 0.53; 95% CI, (0.43–0.66); *P* < 0.0001 HR, 0.41; 95% CI, (0.20–0.82); *P* = 0.012 HR, 0.54; 95% CI, (0.43–0.67); *P* < 0.0001 Dapagliflozin group had higher eGFR compared to placebo *P* < 0.001 Dapagliflozin group had lower UACR compared to placebo *P* < 0.001
VERTIS CV (2020, 2021)[87,135] **(NCT01986881)**	T2DM Established ASCVD eGFR ≥30 ml/min/1.73 m^2	8 246	166 (3)	Ertugliflozin 5 mg vs ertugliflozin 15 mg vs matched placebo once daily (1:1:1)	3	Composite of death from CV causes, MI, or stroke HR, 0.97; 95.6% CI, (0.85–1.11); *P* < 0.001 (for non-inferiority)	Composite kidney outcome event of death from kidney causes, KRT, or doubling of the serum creatinine level from baseline	HR, 0.81; 95.8% CI, (0.63–1.04)

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
						Death from CV causes or hospitalization for HF 8.1% vs 9.1% (ertugliflozin vs placebo) HR, 0.88; 95.8% CI, (0.75–1.03); *P* = 0.11 (for superiority)	Composite kidney outcome of sustained 40% reduction from baseline in eGFR, chronic kidney dialysis/transplant or kidney death (events per 1000 person-years)	Ertugliflozin vs placebo 6.0% vs. 9.0%; HR, 0.66; 95% CI, (0.50–0.88)
						Death from CV causes HR, 0.92; 95.8% CI, (0.77–0.11)	Change in eGFR (relative to baseline)	2.6 ml/min/1.73m^2
							change in UACR (relative to baseline)	-16.2%
SCORED (2021)[136] **(NCT03315143)**	Patients with T2DM and CKD, with or without albuminuria HbA1c level: ≥7%; eGFR: 25 to 60 ml/min/1.73 m^2	10 584	176 (3.3)	Sotagliflozin 200 mg to 400 mg once daily vs matched placebo (1:1)	1.3	CV death, hospitalizations for HF, and urgent visits for HF 5.6 vs 7.5 (no. of events/100 patient-years) HR, 0.74; 95% CI, (0.63–0.88); *P* < 0.001	First occurrence of sustained decline in eGFR ≥50% from baseline for at least 30 days, long-term dialysis, KRT, or sustained eGFR <15 ml/min/1.73 m^2 for ≥ 30 days	Sotagliflozin vs placebo 0.5% vs 0.7%; HR, 0.71; 95% CI, (0.46–1.08)

Trial Name	Key eligibility criteria	Sample size (N)	African Race N (%)	Intervention	Median follow-up period (Years)	CV outcomes	Kidney endpoints	Outcomes
	Risk for CV disease							
EMPA-KIDNEY (2023)[91] **(NCT03594110)**	Patients with CKD eGFR: ≥20 to <45 ml/min/1.73 m^2 or ≥45 to <90 ml/min/1.73 m^2 UACR: ≥200 mg/g	6 609	128 (4)	Empagliflozin 10 mg daily vs matched placebo once daily (1:1)	2	CV death, hospitalization for HF 4.0% vs 4.6% (Empagliflozin vs placebo)	Progression of kidney disease (KF, sustained decrease in eGFR to <10 ml/min/1.73 m^2, stained decrease in eGFR of ≥40% from baseline, or kidney death) or death from CV events	Empagliflozin group vs placebo 13.1% vs 16.9%; HR, 0.72; 95% CI, (0.64–0.82); $P < 0.001$

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; KF, kidney failure; KRT, kidney replacement therapy; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio

Table 3: Mitigation strategies for adverse events associated with the use of SGLT2is

Adverse risks	Mitigation strategies
Genital infections	• Prior to prescribing SGLT2is, patients should be informed about the risk of genital infections • Patient counseling to maintain good genital hygiene • Patients' education about the signs and symptoms of genital infections • If a patient develops an uncomplicated fungal infection, discontinuation of SGLT2is is not required; rather management with antifungal medications • For those with a history of recurring genital infections, prophylactic antifungal treatment is recommended (to be reviewed after 6 months or earlier if needed)
UTI	• Discontinue SGLT2is when treating pyelonephritis or urosepsis • Caution should be taken when prescribing SGLT2is to a patient with recurrent UTI
DKA	• Prior to initiating SGLT2is, assessment of predisposing factors for DKA • Discontinue SGLT2is, if a patient develops DKA • Patient education about signs/symptoms to help early detection of DKA • Follow-up with blood or urine ketones in high-risk individuals • Sick-day protocol • Restriction on the ketogenic diet, alcohol abuse • Maintaining a minimum low dose of insulin if needed • Consider temporarily stopping SGLT2is, if one chooses intermittent fasting (e.g. for Ramadan) • Undertaking ketone testing for diabetic patients, if unwell • Exercise caution when starting SGLT2is in patients with T1DM and T2DM (consult diabetologist, if needed) • Discontinue SGLT2is for 3 days before surgery or during acute illness
Volume depletion	• Discontinuation of SGLT2is is not required • Regular monitoring of volume status and kidney function • Dose adjustment of diuretics in high-risk patients • Temporarily withhold SGLT2is during acute illness
AKI	• Careful interpretation of initial decline in eGFR after initiating SGLT2is, considering expected drug effect to avoid unwarranted discontinuation of treatment
Amputations	• Routine preventive foot care measures for those at high risk of amputation • Avoid initiating SGLT2is in the presence of active foot infection or ulceration • Discontinue SGLT2is, if foot complications occur during treatment • Consider re-initiating SGLT2i therapy after complete resolution of foot complications
Fractures	• For patients with CKD treated with SGLT2is, monitoring of bone parameters (calcium, phosphate, and PTH) as appropriate for the CKD stage

AKI, acute kidney injury; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection

Figure Legends

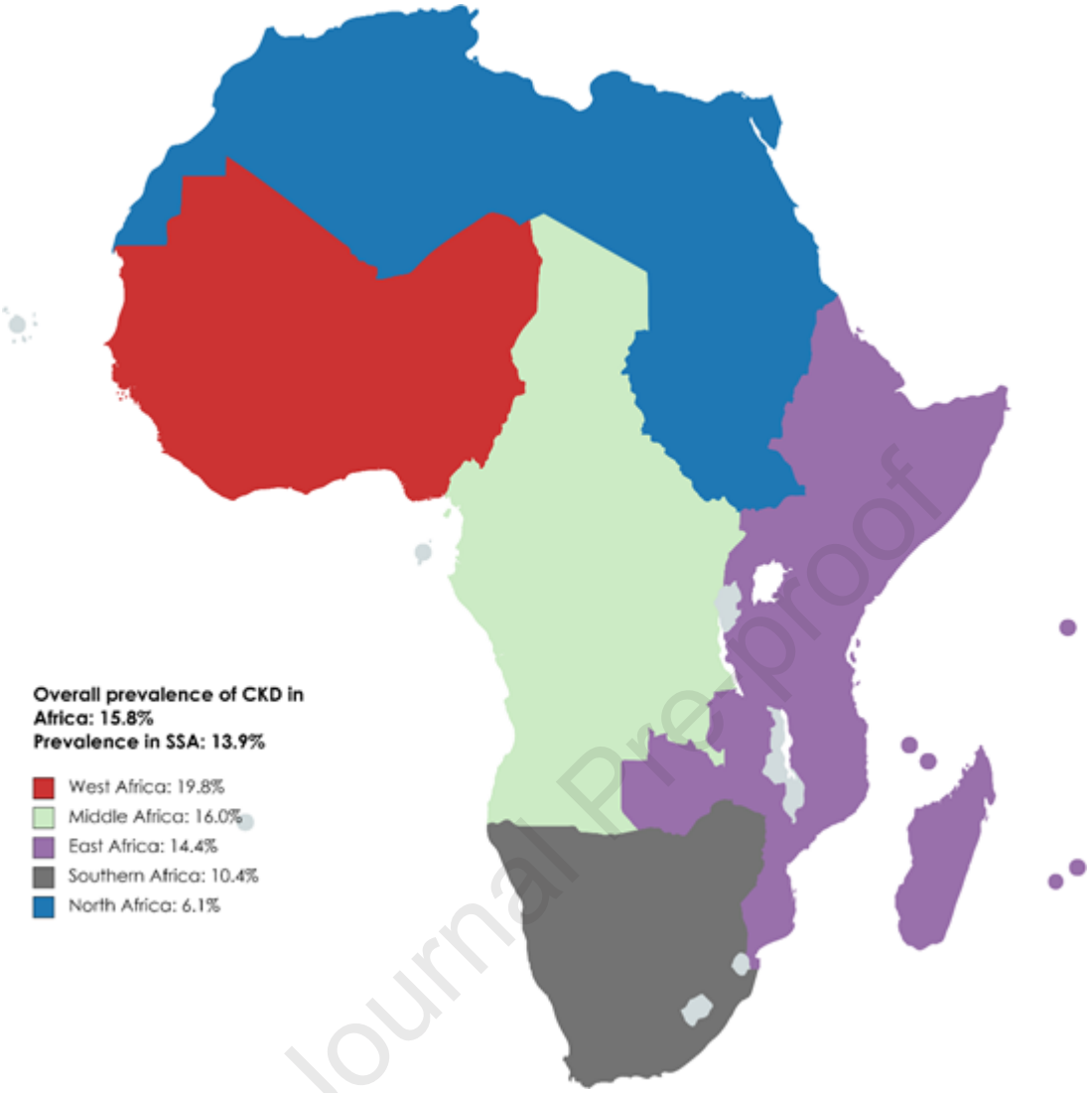
Figure 1. Overall prevalence of CKD in Africa. Adapted from Stanifer JW, Jing B, Tolan S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(3):e174-181. doi:10.1016/S2214-109X(14)70002-6;[16] Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC Nephrol. 2018;19(1):125. doi:10.1186/s12882-018-0930-5;[18]

Figure 2. Identification and referral pathway for the management of CKD. ACEi, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; MBD, mineral bone diseases; RAASi, renin-angiotensin aldosterone system inhibitors; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitors; UACR, urine albumin-to-creatinine ratio. [a]eGFR categories in CKD classification G1: ≥90 ml/min/1.73m^2, G2: 60–89 ml/min/1.73m^2, G3a: 45–59 ml/min/1.73m^2, G3b: 30–44 ml/min/1.73m^2, G4: 15–29 ml/min/1.73m^2 and G5: <15 ml/min/1.73m^2 (kidney failure); [b]UACR categories in CKD classification A1: <30 mg/g, A2: 30-300 mg/g, A3: >300 mg/g. Recreated with permission from Shlipak MG, Tummalapalli SL, Boulware LE, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2021;99(1):34-47. doi:10.1016/j.kint.2020.10.012;[57] permission conveyed through Copyright Clearance Center, Inc.

Figure 3. Mode of action of SGLT2is and beneficial effects.

Figure 4. Delayed risk of KF with the addition of SGLT2is to RAAS blockers. Reproduced from Meraz-Muñoz AY, Weinstein J, Wald R. eGFR Decline after SGLT2 Inhibitor Initiation: The Tortoise and the Hare Reimagined. Kidney360. 2021;2(6):1042-1047. doi:10.34067/KID.0001172021.[70]

Figure 5: Proposed treatment algorithm for SGLT2i therapy in patients with CKD. AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycosylated Hemoglobin; RAASi, renin-angiotensin aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylureas; UACR, urine albumin-to-creatinine ratio. *Refer to Box C for more details. Recreated with permission from Yau K, Dharia A, Alrowiyti I, et al. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney Int Rep. 2022;7(7):1463-1476. doi:10.1016/j.ekir.2022.04.094;[62] permission conveyed through Copyright Clearance Center, Inc.



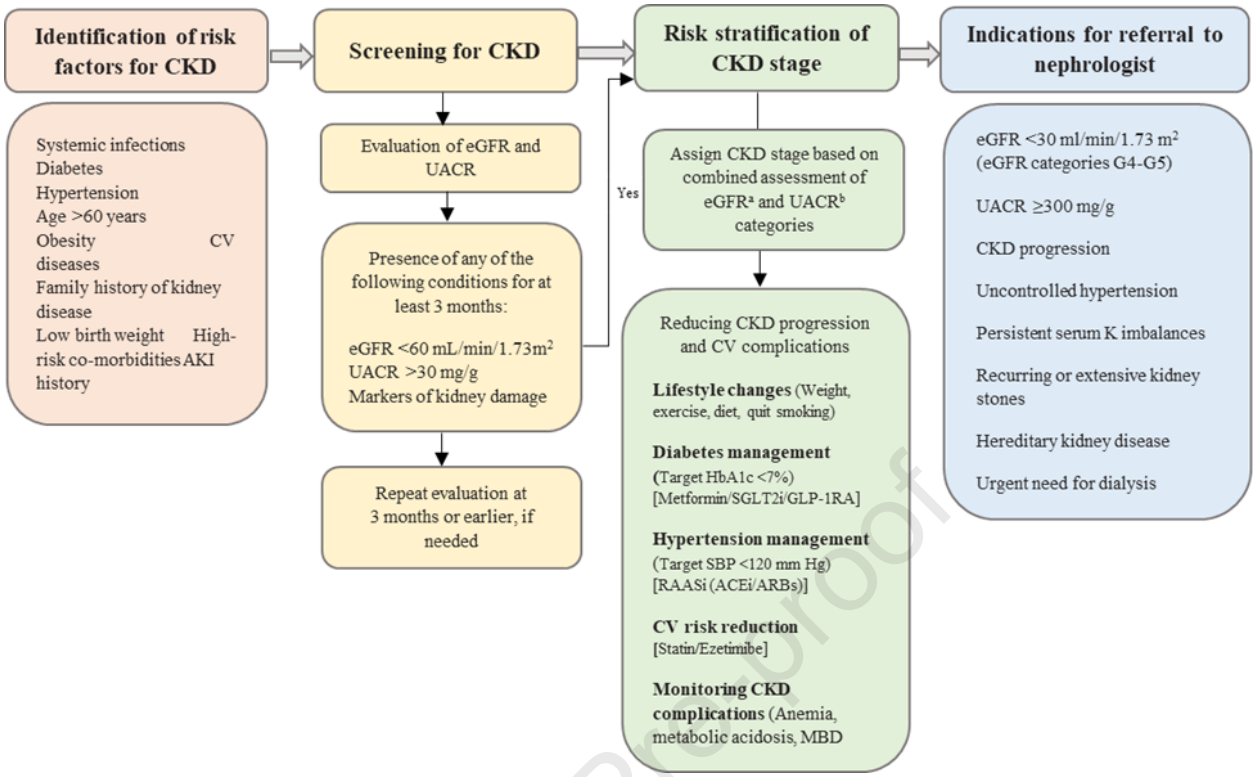


Figure 3. Mode of action of SGLT2is and beneficial effects.