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REVIEW

Emerging Role of Sodium–Glucose Co-Transporter 2 Inhibitors for the Treatment of Chronic Kidney Disease

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Abstract: Chronic kidney disease is one of the leading causes of morbidity and mortality in the Philippines. It is associated with a growing health burden as many patients progress to end-stage renal disease. Until recently, therapeutic options for the management of chronic kidney disease were limited. Sodium–glucose co-transporter 2 inhibitors offer an alternative therapeutic approach for patients with chronic kidney disease. Several trials have shown renal benefits with sodium–glucose co-transporter 2 inhibitors in patients with cardiovascular disease with and without type 2 diabetes and across a range of estimated glomerular filtration rate levels. In the Philippines, the sodium–glucose co-transporter 2 inhibitors dapagliflozin and canagliflozin are approved for the prevention of new and worsening nephropathy in type 2 diabetes. With emerging treatment options, an urgent need exists for guidance on the management of chronic kidney disease within the Philippines. In this review, we focus on the putative renal-protective mechanisms of sodium–glucose co-transporter 2 inhibitors, including effects on tubuloglomerular feedback, albuminuria, endothelial function, erythropoiesis, uric acid levels, renal oxygen demand, and hypoxia. Furthermore, we discuss the findings of recent large clinical trials using sodium–glucose co-transporter 2 inhibitors in patients with chronic kidney disease and diabetic kidney disease, summarize safety aspects, and outline the practical management of patients with chronic kidney disease in the Philippines.

Keywords: chronic renal insufficiency, diabetic nephropathies, safety, sodium-glucose transporter 2 inhibitors

Introduction

Globally, chronic kidney disease (CKD) exerts a major patient and public burden, affecting almost 843.6 million individuals.[1,2] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are the predominant pharmacological interventions available for the treatment of diabetic kidney disease (DKD) and non-DKD, albeit with limitations.[3,4] Concomitant treatment with an ACE inhibitor and ARB is associated with an increased risk of adverse events in patients with diabetic nephropathy.[5] A meta-analysis of 22 randomized controlled trials reported that both ACE inhibitors and ARBs increased the risk of developing hyperkalaemia in patients with CKD stages 3–5 with a glomerular filtration rate (GFR) of <60 mL/min per 1.73 m^2 and elevated serum creatinine levels.[4] Only 52–81% of the patients with CKD stages 3–5 receive renin–angiotensin system (RAS) blockers.[6]

Despite available treatments, the global annual incidence of end-stage renal disease (ESRD) among patients with diabetes had increased from 375.8 to 1016.0 per million during 2000–2015, according to the latest published data.[7] During this period, the incidence of ESRD increased dramatically in Southeast Asia, and this region was reported as having the second highest incidence of ESRD globally.[7] Strict blood glucose with anti-diabetic therapies and blood pressure control by inhibition of angiotensin has been shown to be unable to stop disease progression to ESRD.[8,9] Therefore, new alternative treatment strategies are needed to effectively treat patients with CKD.

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Sodium–glucose co-transporter 2 (SGLT2) inhibitors have evolved from a novel hypoglycemic agent, to potent cardio- and renoprotective agent in type 2 diabetes (T2D), and recently, to an effective standalone therapeutic option for CKD regardless of the presence of diabetes mellitus (DM).[9] SGLT-2 is predominantly expressed in the proximal renal tubule, and accounts for 90% of renal glucose reabsorption. By inhibiting SGLT2, the glucose and sodium reabsorption is decreased, the tubule-glomerular feedback is restored and the aforementioned damage is undone.[10] Large-scale cardiovascular outcome trials investigating SGLT2 inhibitors have demonstrated that these therapies have renoprotective effects distinct from their glucose-lowering action, including the potential to reduce ESRD and acute kidney injury rates.[11,12] Recent studies conducted in patients with moderate-to-severe CKD, SGLT2 inhibitors (canagliflozin, dapagliflozin) showed renoprotective effects.[12,13] SGLT2 inhibitors therefore represent an alternative or adjunct to current treatment approaches in the management of CKD in patients with and without T2D. In the Philippines, dapagliflozin is approved for the prevention of new and worsening nephropathy in T2D, and canagliflozin is approved for use in patients with CKD and albuminuria.[14,15] Due to the continuous increase in the number of patients progressing to ESRD from diabetes mellitus,[7] an urgent need for guidance on the management of CKD within the Philippines exists, especially with emerging treatment options. The aim of this manuscript is to review the epidemiology of CKD in Philippines and recent large clinical-outcome trials of SGLT2 inhibitors in patients with CKD, putative renal-protective mechanisms of action of SGLT2 inhibitors, and the practical management of patients with CKD.

Epidemiology of CKD in the Philippines

The prevalence of CKD in Asia was estimated to be 434.3 million (95% confidence interval (CI) 350.2 to 519.7) in a recent systematic review and meta-analysis.[16] The average prevalence of CKD stages 3–5 in Asia was 11.2%; the prevalence of CKD stages 3–5 varied among subregions (East Asia: 8.6%, South-East Asia: 12.0%, Western Asia: 13.1%, South Asia: 13.5%.[17] In 2017, the prevalence of CKD in Southeast Asia was almost 70 million people.[1] Asian patients with T2D have high rates of kidney disease,[18,19] with 58.6% having microalbuminuria or macroalbuminuria.[18] Furthermore, a higher proportion of Southeast Asian patients with T2D develop nephropathy and progressive kidney failure at a much younger age than their European counterparts.[19] A study conducted in Manila reported a high prevalence (42%) of nephropathy among patients newly diagnosed with T2D.[20] A recent retrospective study conducted by Crisostomo and Allyn Sy has also reported high nephropathy rate (about 40%) in patients with newly diagnosed with T2D.[21] In 2017, the prevalence of CKD in the Philippines was 9,317,802, with 34,051 CKD-attributed deaths.[1] In 2019, CKD was the fourth leading cause of mortality in the Philippines.[22] According to a 2015 systematic review, the use of renal replacement therapy (RRT) in Asia is expected to rise sharply in the next decade.[23]

According to the latest World Health Organization data published in 2020 Kidney Disease Death rate in Philippines reached 51.96% or 5.84% of the total deaths.[24] A database including current data on CKD is unavailable in the Philippines. CKD management in the Philippines is an important issue yet is limited by a paucity of published data on CKD. The Philippine Renal Disease Registry, with most recent data from 2016, for example, predominantly reports RRT data, underscoring the rising number of patients receiving dialysis but not including data on patients with CKD stages 1 to 4.[25] According to Philippine Renal Disease Registry 2020 Annual report, in 2016, the incidence and prevalence of patients undergoing dialysis for ESRD in the Philippines was 21,535 and 37,280, respectively.[25] By 2025, the number of patients with ESRD in the Philippines is expected to increase by 10–20%.[26] According to a 2019 report, PhilHealth (a national health insurance program) spent over 10.6 billion Philippine pesos for 2,187,846 haemodialysis claims, which ranked first among the top 10 medical procedures.[27] These data underscore the incredible burden of RRT and the need for treatments that can mitigate CKD progression, which could help offset the high costs of RRT.[2]

Data on Filipino patients with CKD are scarce, but a single-centre study on CKD education reported that among 299 financially disadvantaged patients with CKD, 60% were men, mean age was 49 years, and 37% were high-school graduates.[28] A total of 30% of the patients had chronic glomerulonephritis as the primary renal disease, and 60% initially presented to the tertiary renal referral centre with CKD stage 5. When evaluated prior to consultation at the study site, 43.1% of the patients did not know about the seriousness of CKD, and 17.7% thought CKD was not serious.[28] Overall, these data suggest a gap in the screening and diagnosis of CKD in the Philippines that warrants further study.

Background on SGLT2 Inhibitors

In healthy individuals, the kidneys play an important role in glucose homeostasis through gluconeogenesis and the active reabsorption of nearly all the glucose filtered by the glomerulus.[29] Sodium–glucose co-transporters significantly contribute to renal glucose reabsorption. SGLT1 is a high-affinity, low-capacity transporter responsible for a small proportion of the renal glucose reabsorption; it is primarily located in the small intestine but is also found in the S3 segment of the renal proximal tubule (PT) and other tissues.[30–33]

SGLT2 is a low-affinity, high-capacity transporter responsible for most of the renal glucose reabsorption; it is located in the S1 and S2 segments of the renal PT.[31–34] When initially approved, SGLT2 inhibitors were contraindicated in patients with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 because of their decreased glucose-lowering efficacy with decreasing kidney function, reflecting their mode of action.[35] Since then, numerous trials have demonstrated renal benefits with various SGLT2 inhibitors in patients with T2D with and without CKD and with various types of cardiovascular disease (CVD), supporting their use in patients with eGFR ≥30 mL/min per 1.73 m^2.[13,36] In the Philippines, dapagliflozin was recently approved for the prevention of new or worsening nephropathy in patients with T2D with eGFR ≥45 mL/min per 1.73 m^2.[14]

Various American (eg, American Diabetes Association,[37] American College of Cardiology[38]), European (eg, European Society of Cardiology, European Association for the Study of Diabetes[39]), and global (eg, Kidney Disease: Improving Global Outcomes[40]) guidelines recommend the use of SGLT2 inhibitors in patients with CKD and T2D. Given the very recent publication of some large clinical-outcome trials of SGLT2 inhibitors (Table 1), some guidelines remain to be updated based on the results of those trials, particularly for patients with CKD without T2D. For example, the latest CKD guidelines from the European Renal Association—European Dialysis and Transplant Association are from 2016.[41] There is increasing activity aimed at developing local guidelines in Asia (Japan, China, Korea, the Philippines, and Indonesia).[42] The Asian Pacific Society of Nephrology Clinical Practice Guideline on Diabetic Kidney Disease recommends the use of SGLT2 inhibitors in adults with T2D and eGFR ≥30 mL/min per 1.73 m^2 who have DKD or CVD.[43] In the completed clinical-outcome trials, renal benefits of SGLT2 inhibitors were demonstrated at decreasing levels of baseline kidney dysfunction (as reflected by varying levels of eGFR and albuminuria), independent of the glucose-lowering effects of SGLT2 inhibitors, the presence of T2D, or the use of RAS blockers.[13,44–47]

Potential Renal-Protective Mechanisms of SGLT2 Inhibitors

Various mechanisms that could explain the beneficial renal effects of SGLT2 inhibitors have been postulated and reviewed.[30,48] Although clinical trial data support the existence of renal-protective mechanisms with SGLT2 inhibition, given the complexity and number of potential mechanisms involved, caution should be exercised in attributing the beneficial renal effects of SGLT2 inhibitors to any single mechanism. The proposed mechanisms, which include direct effects on renal physiology and anti-inflammatory, anti-hypertensive, and anti-fibrotic effects,[48] may work synergistically, with some mechanisms contributing to a greater extent under certain clinical settings. The schematic diagram on potential renal-protective mechanisms of SGLT2 inhibitors is presented in Figure 1.[49]

Insight into some of the mechanisms of SGLT2 inhibition was provided by the randomized, placebo-controlled, multicentre DIAMOND study, which examined the effects of 6 weeks of treatment with dapagliflozin on proteinuria in patients with non-diabetic CKD and residual proteinuria.[50] Dapagliflozin did not reduce glycated haemoglobin, proteinuria, or fasting plasma glucose and did not affect urine adenosine or other vasoactive mediators. The 6-week timeframe of DIAMOND was probably too short for the reduced glomerular pressure caused by SGLT2 inhibition to affect proteinuria.[50] Dapagliflozin did affect body weight and haemoconcentration biomarkers, and reduced measured GFR, which was completely reversible within 6 weeks of drug discontinuation.[50] This suggests SGLT2 inhibition ameliorates kidney function, independent of its glycaemic effects. Further mechanistic research is anticipated, especially given the important differences in pathogenic mechanisms between DKD and non-DKD.[51]

Table 1 Randomized, Double-Blind Clinical Trials of SGLT2 Inhibitors with Renal Outcomes

Trial	SGLT2 Inhibitor	Population	Number Randomized	Median Duration	Renal Inclusion Criteria	Renal Parameters at Baseline[a]	Renal Outcomes
EMPA-REG OUTCOME[69,70]	Empagliflozin	T2D with CVD	7028	2.6 years (treatment)	eGFR ≥30 (by MDRD equation)	eGFR 45–59 in 18%, 30–44 in 8%; microalbuminuria, 29%; macroalbuminuria, 11% 81% taking ACE inhibitors or ARBs	Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 patients (18.8%) in the placebo group (HR in the empagliflozin group, 0.61; 95% CI, 0.53–0.70; P < 0.001) Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 patients (2.6%) in the placebo group, a significant relative risk reduction of 44%
EMPEROR-Reduced[76]	Empagliflozin	Chronic HF (NYHA functional class II–IV) with left ventricular ejection fraction ≤40% in both study groups; T2D in 50%	3730	16 months (follow-up)	eGFR <60 or ≥60 (by CKD-EPI equation)	eGFR <60 in 48%; mean eGFR ~62 71% (empagliflozin) and 69% (placebo) received ACE inhibitors or ARBs (without a neprilysin inhibitor)	Composite renal outcome (chronic dialysis/renal transplantation/a profound, sustained reduction in eGFR) occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (HR, 0.50; 95% CI, 0.32–0.77)
CANVAS Program[71,72]	Canagliflozin	T2D with high CV risk	10,142	126.1 weeks (follow-up)	eGFR ≥30[b] Albuminuria category not specified as an exclusion or inclusion criterion, with the exception of those participants aged ≥50 years for whom micro- or macroalbuminuria could be one of two or more required risk factors out of a list of several possibilities	Mean eGFR 77; median UACR 12; 23% had microalbuminuria, 8% had macroalbuminuria RAS inhibitor use for all participants not reported, though 81% of participants with eGFR <90 were treated with RAS inhibitors	Composite outcome of 40% sustained decrease in eGFR, need for RRT or death from renal causes occurred less frequently in the canagliflozin group compared with the placebo group (5.5 vs 9.0 per 1000 patient-years in the canagliflozin and placebo groups, respectively; HR 0.60; 95% CI, 0.47–0.77)

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CREDENCE[b12]	Canagliflozin	T2D and albuminuric CKD	4401	2.62 years (follow-up)	eGFR 30 to <90 (by CKD-EPI equation) and UACR >300 to 5000, as measured in a central laboratory	Mean eGFR was 56; median UACR was 927 99.9% treated with RAS inhibitors	Relative risk of composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15) was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR, 0.70; 95% CI, 0.59–0.82; P = 0.00001)
DAPA-HF[75]	Dapagliflozin	HF with left ventricular ejection fraction ≤40%; NYHA functional class II–IV; with/ without T2D	4742	18.2 months (follow-up)	eGFR ≥30 (by CKD-EPI equation); albuminuria not assessed	eGFR <60 in 41% 80% of participants with eGFR <60 and 86% with eGFR ≥60 were treated with ACE inhibitors or ARBs	The composite renal outcome (major components: ≥50% decline in eGFR and need for sustained dialysis) was not significantly reduced by dapagliflozin (HR, 0.71; 95% CI, 0.44–1.16; P = 0.17); doubling of serum creatinine occurred in 1.8% with dapagliflozin vs 3.2% with placebo (HR, 0.56; 95% CI, 0.39–0.82; P=0.003); rate of decline in eGFR (between days 14 and 720) was less with dapagliflozin, −1.09 (95% CI, −1.41 to −0.78) vs placebo −2.87 (95% CI, −3.19 to −2.55) per year (P < 0.001). This was observed in those with/without T2D (P for interaction = 0.92)
DECLARE-TIMI 58[73]	Dapagliflozin	T2D with established atherosclerotic CVD or CVD risk factors	17,160	4.2 years (follow-up)	CrCl <60 mL/min (Chronic Kidney Disease Epidemiology Collaboration equation); albuminuria not mentioned	Mean eGFR was 85; 45% of patients had an eGFR 60–90. As a result of the exclusion criterion for CrCl at screening, only 7% had an eGFR <60 at randomization 81% received ACE inhibitors or ARBs	A renal event occurred in 4.3% of patients in the dapagliflozin group and in 5.6% of patients in the placebo group (HR, 0.76; 95% CI, 0.67–0.87)

(*Continued*)

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Table 1 (Continued).

Trial	SGLT2 Inhibitor	Population	Number Randomized	Median Duration	Renal Inclusion Criteria	Renal Parameters at Baseline[a]	Renal Outcomes
DAPA-CKD [c13]	Dapagliflozin	Patients with CKD, with/without T2D	4304	2.4 years (follow-up)	eGFR ≥25 and ≤75[b]; UACR ≥200 and ≤5000 All participants were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks before screening, except those unable to take ACE inhibitors or ARBs	Mean eGFR was ~43; median UACR was 965 (dapagliflozin), 934 (placebo) 31% (dapagliflozin) and 32% (placebo) received ACE inhibitors; 67% (dapagliflozin) and 66% (placebo) received ARBs	Primary outcome (composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes) event occurred in 197 of 2152 patients (9.2%) in the dapagliflozin group and 312 of 2152 patients (14.5%) in the placebo group (HR, 0.61; 95% CI, 0.51–0.72; P < 0.001; NNT to prevent one primary outcome event, 19 [95% CI, 15–27])
SCORED[83]	Sotagliflozin	T2D with CKD and CVD risk factors	10,584	16 months (follow-up)	eGFR 25–60[b]; no requirement for macro- or microalbuminuria	Median eGFR was 45; median UACR was 74 89% (sotagliflozin) and 88% (placebo) received any RAS inhibitor	In patients with baseline eGFR ≥30, 37 events in the sotagliflozin group and 52 events in the placebo group (HR, 0.71; 95% CI, 0.46–1.08) of first occurrence of a sustained ≥50% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant or sustained eGFR <15 (for ≥30 days) were reported
VERTIS[82,104]	Ertugliflozin	T2D with atherosclerotic CVD	8246	3.0 years (follow-up)	eGFR ≥30 (by MDRD); albuminuria not mentioned	Mean eGFR was ~76 81% (ertugliflozin) and 82% (placebo) of patients received RAS inhibitors	HR for death from renal causes, RRT, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63–1.04)

Notes: [a]Unless otherwise specified, values are for the treatment and placebo groups combined. [b]Equation used to assess eGFR was not specified. [c]Renal outcomes were primary endpoints. For all other trials, renal outcomes were secondary endpoints. eGFR is expressed as mL/min per 1.73 m^2; UACR is expressed as mg/g.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, Creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; NNT, number needed to treat; NYHA, New York Heart Association; SGLT2, sodium–glucose co-transporter 2; RAS, renin–angiotensin system; RRT, Renal replacement therapy; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

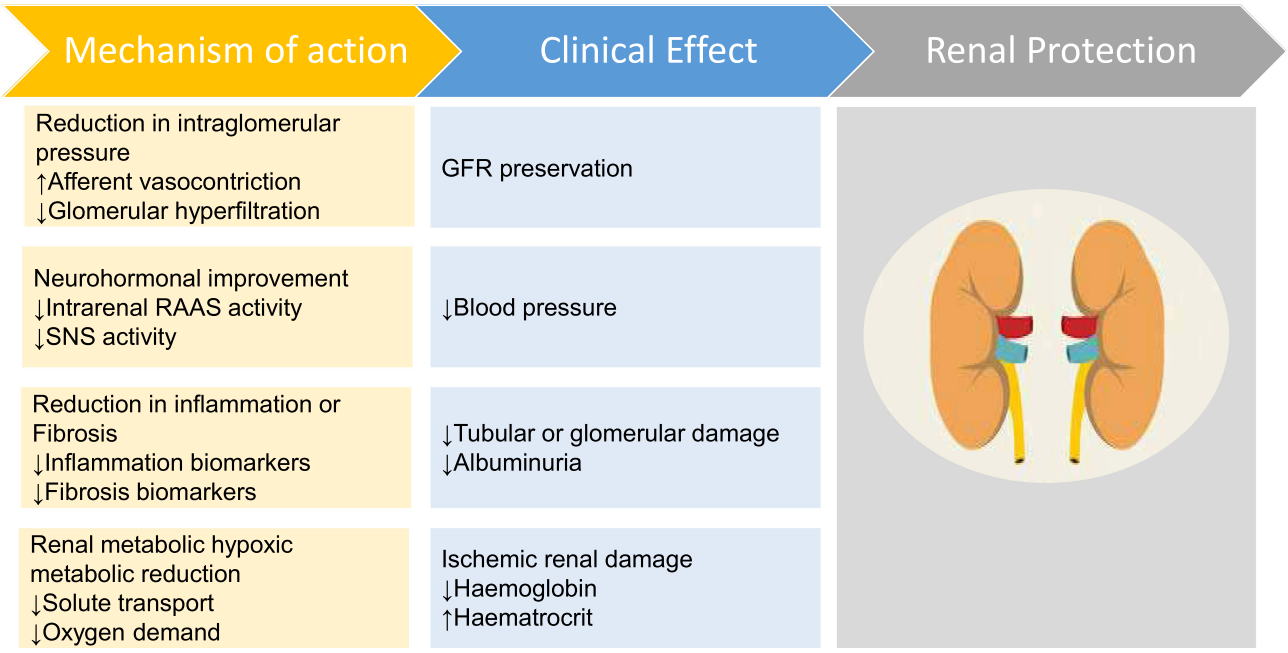

Figure 1 Schematic diagram on potential renal-protective mechanisms of SGLT2 inhibitors.
Notes: The up and down arrows in white boxes indicate an increase and decrease, respectively. Adapted from Leoncini G, Russo E, Bussalino E, Barnini C, Viazzi F, Pontremoli R. SGLT2is and renal protection: from biological mechanisms to real-world clinical benefits. Int J Mol Sci. 2021;22(9):4441. doi:10.3390/ijms22094441.[49]
Abbreviations: GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Tubuloglomerular Feedback

In diabetes, increased glucose and sodium reabsorption in the renal PT leads to increased adenosine triphosphate (ATP) and oxygen demand.[45,52] Adenosine is an important signalling factor for tubuloglomerular feedback (TGF) at the macula densa (MD).[53] Excessive sodium reabsorption in the renal PT also leads to decreased sodium delivery to the MD.[54] This decreases the adenosine production due to reduced consumption of ATP at the MD, and therefore reduces TGF, leading to increased glomerular pressure or RAS activity. SGLT2 inhibition increases sodium delivery to the MD,[54] thereby increasing the ATP consumption and adenosine production.[55] The increase in adenosine causes vasoconstriction of the afferent arteriole, leading to a reduction in intraglomerular hypertension and a decrease in eGFR.[30,35,54–56] Overall, by promoting specific intrarenal haemodynamic changes, SGLT2 inhibitors may protect glomeruli from barotrauma.[45,48]

Albuminuria

Reductions in albuminuria may also offer protection against renal damage. Adding dapagliflozin to ACE inhibitor or ARB therapy in hypertensive patients with T2D reduced albuminuria as early as 4 weeks from treatment initiation.[57] However, SGLT2 inhibitors' renal benefits independent of baseline albuminuria, as seen in large clinical trials, suggest that non–albuminuria-lowering mechanisms additionally account for the renal benefits.[47]

Endothelial Function

Endothelial cells are important in not only the vasculature but also the kidney, given the endothelial cells' exposure to the circulation and any toxins. Increased sodium levels can have undesirable effects on vascular contractility by damaging the glycocalyx lining of the endothelial vascular walls and stiffening the vessels.[58,59] SGLT2 inhibition, by lowering blood glucose and sodium levels, reduces aortic stiffness and improves endothelial function, conduit arterial function, and vascular tone.[60,61] Mechanistic studies in patients with T2D demonstrate a direct beneficial effect on the vasculature associated with a decline in markers of oxidative stress.[61] The mechanisms and the extent to which these renal benefits are exerted in patients with CKD without T2D remain to be elucidated.

Erythropoiesis

Treatment with SGLT2 inhibitors transiently increases erythropoietin levels.[56] Mechanisms beyond haemoconcentration, such as reverse renal remodelling, could contribute to the effect on erythropoietin.[62] The increase in haematocrit associated with SGLT2 inhibition may be due to the normalization of renal cortical oxygenation resulting in the normalization of erythropoietin-producing cell function.[62] Further studies are needed to investigate the degree to which the increased haematocrit reported with SGLT2-inhibitor treatment is a safety or efficacy signal.

Uric Acid Levels

Increased serum uric acid levels are associated with high risk for renal diseases and all-cause mortality.[63,64] Hyperuricaemia may trigger proinflammatory cytokines, resulting in vascular and tubulointerstitial lesions, which eventually promote the development of CKD.[65] Additionally, hyperuricaemia induces hypertension by activating the RAS and inhibiting nitric oxide synthesis, promoting endothelial dysfunction, vascular smooth-muscle cell proliferation, and sodium reabsorption. SGLT2 inhibition reduces serum uric acid levels,[66] possibly indirectly via modulation of glucose transporter 9.[63] However, subgroup analyses of a meta-analysis did not show a serum uric acid–lowering effect in patients with CKD.[66]

Renal Oxygen Demand and Hypoxia

Sodium reabsorption drives renal oxygen consumption.[67] SGLT1 and SGLT2 inhibition in diabetic rats has been shown to improve the partial pressure of oxygen in the renal cortex.[68] By inhibiting sodium transport, SGLT2 inhibitors in these rats reduced the workload of the renal PTs and improved tubulointerstitial hypoxia by decreasing the excess renal oxygen requirement,[68] effects that can be potentially extrapolated to humans.

Clinical Trials of SGLT2 Inhibitors in Patients with CKD and DKD

Large, randomized, double-blind, placebo-controlled, cardiovascular-outcome trials in patients with T2D, such as EMPA-REG OUTCOME,[69,70] CANVAS,[71,72] and DECLARE-TIMI 58,[73] initially provided evidence for the renal benefits of various SGLT2 inhibitors (Table 1). In EMPA-REG OUTCOME, empagliflozin slowed the progression of kidney disease, lowered the risk of serum creatinine doubling, and RRT compared with placebo.[69] CANVAS demonstrated a lack of effect modification by baseline eGFR.[72] In DECLARE-TIMI 58, dapagliflozin lowered the rate of progression of renal disease in patients who had or were at risk for atherosclerotic CVD.[73] In a post hoc analysis of this trial, dapagliflozin reduced the risk of hospitalization for heart failure and renal-specific composite outcomes in patients with multiple risk factors for atherosclerotic CVD, suggesting beneficial effects in a broad primary-prevention population.[74] Although these trials showed renal benefits, few patients were at high risk of kidney failure and the studies did not have renal endpoints as the primary outcome.

The DAPA-HF trial, in patients with heart failure with reduced ejection fraction with and without T2D, found that dapagliflozin treatment slowed the rate of eGFR decline, regardless of T2D status or baseline eGFR level.[75] EMPEROR-Reduced, which used a different composite renal outcome and had more renal events than DAPA-HF, also showed a slower rate of eGFR decline, as well as a lower risk of serious renal outcomes, in empagliflozin-treated versus placebo-treated patients.[76] Randomized-controlled-trial evidence for renal benefits with SGLT2-inhibitor treatment was substantiated by the global CVD-REAL 3 observational trial, involving more than 65,000 patients with T2D; compared with other glucose-lowering drugs, treatment with SGLT2 inhibitors was associated with a slower rate of kidney function decline and lower risk of major kidney events.[77]

CREDENCE, the first clinical trial of an SGLT2 inhibitor with a primary renal endpoint, included only patients with T2D and albuminuric CKD on an ACE inhibitor or ARB treatment background and demonstrated a lower risk of kidney failure versus placebo after a median follow-up of 2.62 years (the trial was stopped early because of indications of substantial efficacy).[12]

Given SGLT2 inhibitors' mechanisms of action involving salutary effects on glomerular haemodynamics and not just metabolic parameters, their beneficial renal effects were predicted to extend to patients with CKD that is non-DKD.[78]

This hypothesis was substantiated by the DAPA-CKD trial, which was stopped early because of indications of substantial efficacy after a median follow-up of 2.4 years. DAPA-CKD is the only large, completed clinical trial to date that enrolled patients with CKD with and without T2D (N=4304, including 115 patients from the Philippines). Patients receiving dapagliflozin had a decreased risk of worsening kidney function (defined as ≥50% sustained decline in eGFR), ESRD, or death from renal or cardiovascular causes versus placebo.[13] A greater reduction in eGFR was observed during the first 2 weeks of treatment with dapagliflozin than with placebo. This was followed by a smaller annual change in the mean eGFR. Importantly, renal protection was demonstrated in patients with baseline eGFR as low as 25 mL/min per 1.73 m^2.[13] Given the broad range of countries represented, the results of DAPA-CKD demonstrated that dapagliflozin produces similar beneficial effects on renal outcomes regardless of patients' race and geographic region.[79]

Overall, several meta-analyses have substantiated the benefits of SGLT2 inhibitors on various renal outcomes. A meta-analysis of six trials (EMPA-REG OUTCOME, the two trials of the CANVAS Program, DECLARE-TIMI 58, CREDENCE, and VERTIS CV) suggests favourable effects of SGLT2 inhibitors on kidney disease progression with moderate heterogeneity across trials.[36] Another meta-analysis of data from EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58, and CREDENCE further substantiated the reduced risk of dialysis, transplantation, and death due to kidney disease, as well as protection against acute kidney injury (AKI).[47] In a recent network meta-analysis of 764 trials (CKD and/or albuminuria: 37 trials; high risk of cardiovascular or kidney disease: 10 trials) undertaken in patients with T2D, SGLT2 inhibitors reduced kidney failure (which was generally defined as eGFR <15 mL/min per 1.73 m^2 or start of RRT).[80] A meta-analysis of 12 large trials (T2D: 9 trials including EMPA-REG OUTCOME, CANVAS Program, DAPA-HF, and CREDENCE; without T2D: 3 trials) suggested that the beneficial effects of SGLT2 inhibitors on clinical kidney outcomes were not restricted to patients with T2D.[81] However, whether the beneficial nephroprotective effects extend to all SGLT2 inhibitors remains to be established. Evidence suggests heterogeneity among different SGLT2 inhibitors; for example, the VERTIS CV trial[82] of ertugliflozin and the SCORED trial[83] of sotagliflozin did not find significant differences between SGLT2-inhibitor treatment and placebo on the composite renal outcome. However, multiple factors could have caused these negative results. Heterogeneity among outcomes across the different SGLT2 inhibitors could be attributed to different populations included in the trials, different baseline renal risk, and/or differences in outcome definitions (Table 1).

The varying levels of eGFR and albuminuria in the completed SGLT2-inhibitor trials provide robust evidence supporting their renal benefits across a wide range of types and degrees of kidney dysfunction (Table 1). Although stopping trials early could lead to overestimation of treatment benefits,[84] the confirmatory results across most trials suggest that the beneficial renal-protective effects of SGLT2 inhibition are genuine. EMPA-KIDNEY (NCT03594110)[85] is being conducted in patients with CKD without T2D. Estimated to complete by the end of 2022, it has a composite primary endpoint of time to first occurrence of kidney disease progression or cardiovascular death. The results of EMPA-KIDNEY may support the results of DAPA-CKD and DECLARE-TIMI 58 and will add to the evidence base on the use of SGLT2 inhibitors in patients with CKD.

The Safety of SGLT2 Inhibitors and Practical Management of Patients with CKD

Current criteria for diagnosis of CKD in adults (irrespective of age) include persistent signs of renal damage (for at least 3 months), such as a eGFR <60 mL/min per 1.73 m^2 or increased urine albumin-to-creatinine ratio.[86] This approach has been critiqued, because it the threshold for diagnosis of CKD is less accurate particularly in older people.[87,88] Older people with eGFR 45 to 59 mL/min/1.73 m^2 are not necessarily at low risk of CKD complications.[88] A large meta-analyses conducted (2,051,244 participants) to evaluate association between the age and eGFR and albuminuria indicated that the eGFR threshold above which the risk of mortality is increased is not consistent across all ages.[89] Among younger individuals, mortality is increased at eGFR <75 mL/min per 1.73 m^2, whereas in elderly people it is increased at levels <45 mL/min per 1.73 m^2.[89]

Different clinical trials used different eGFR thresholds for inclusion of participants (Table 1). The lowest approved eGFR to start canagliflozin and empagliflozin treatment is ≥30 mL/min per 1.73 m^2 and ≥45 mL/min per 1.73 m^2, respectively.[15,90] In DAPA-CKD, dapagliflozin was prescribed in 979 (45.5%) patients with eGFR 30 to <45 mL/min per 1.73 m^2, and in 293 (13.6%) patients with eGFR <30 mL/min per 1.73 m^2.[13] In CREDENCE, 119 (5.4%) patients with

eGFR between 30 and <45 mL/min per 1.73 m^2 received canagliflozin.[12] We therefore recommend further evaluation of the appropriate eGFR threshold for which SGLT2 inhibitors can be used.

A common phenomenon from the clinical trials that should not be mistaken for an adverse event (and that does not signify an increased risk of an adverse event) is the slight reduction in eGFR (the "eGFR dip") that occurs within the first few weeks of initiation of SGLT2-inhibitor treatment.[44] The eGFR dip, typically between 4 and –6 mL/min per 1.73 m^2,[48] is transient and reversible within a few weeks of treatment discontinuation,[50] even after ~3 years of treatment.[69] Rather than an indication of lack of efficacy, the eGFR dip is generally thought to signify that the medication is working; it reflects acute haemodynamic effects, marked by initial reduction in hyperfiltration, and, in the long term, preservation of kidney structure and improved renal clinical outcomes.[44] The eGFR dip has been seen across many large clinical trials, indicating a class-wide effect and one independent of the presence of T2D or severity of baseline kidney dysfunction.[44] A post hoc analysis of the EMPA-REG OUTCOME trial found that patients with T2D and more advanced kidney disease and/or diuretic therapy at baseline had a greater chance of having an initial eGFR dip >10%, which occurred in 28.3% of the patients on empagliflozin and 13.4% of the patients on placebo.[91] Additionally, a post hoc analysis of the CREDENCE trial reported that significantly more patients with T2D and CKD experienced an eGFR dip >10% in the canagliflozin (45%) than in the placebo group (21%).[92] However, large, prolonged fluctuations in serum creatinine warrant evaluation for AKI.[93] SGLT2 inhibitors induce a natriuretic response, which may restore TGF and reduce intraglomerular pressure.[30]

SGLT2 inhibitors have been shown to be generally safe, although they confer a higher risk of mycotic genital infections and diabetic ketoacidosis (DKA) compared with placebo.[36] The risk of mycotic genital infections can be reduced with appropriate hygiene.[94] A meta-analysis did not find an increased risk of AKI, DKA, urinary tract infection, or fracture compared with active comparators or placebo.[95] Indeed, in a network meta-analysis, SGLT2 inhibitors were associated with a lower risk of AKI compared with placebo and active comparators.[96] Although reports of AKI were initially a concern with SGLT2-inhibitor treatment, current evidence supports a renal-protective effect.[47,97,98] In the DAPA-CKD trial, there were no cases of definite or probable DKA in the dapagliflozin group versus 2 cases in the placebo group.[13] Severe hypoglycaemia—characterized by severe impairment in consciousness or behaviour and the need for external assistance and intervention to treat hypoglycaemia—was observed in half the number of patients in the dapagliflozin group compared with those in the placebo group (14 vs 28), but was not observed in patients with non-diabetic CKD.[13] At low plasma glucose levels, the efficacy of SGLT2 inhibitors to increase urinary glucose excretion is attenuated, resulting in a low risk of hypoglycaemia.[30] However, a multicentre cohort study undertaken in the United Kingdom and Canada in patients with T2D compared dipeptidyl peptidase-4 inhibitors with SGLT2 inhibitors and found the latter to be associated with almost a threefold greater risk of DKA.[99] DKA is a medical emergency and when associated with SGLT2-inhibitor treatment can present with euglycaemia, which could delay diagnosis.[100] The occurrence of euglycaemia depends on the balance between endogenous glucose production and renal glucose clearance. DKA symptoms include nausea, vomiting, abdominal pain, thirst, polyuria, fever, and confusion.[100] To prevent SGLT2 inhibitor–mediated DKA, SGLT2-inhibitor treatment should be stopped during excessive alcohol intake, dehydration, acute illness, ~3 days before surgery, or in situations associated with volume depletion such as diarrhoea and vomiting, and insulin omission or inappropriate dose reduction should be avoided.[100] The Asian Pacific Society of Nephrology Clinical Practice Guideline on Diabetic Kidney Disease recommends that screening for blood ketone levels be performed in individuals taking SGLT2 inhibitors during starvation, excessive alcohol intake, acute illness, or inappropriate insulin dose reduction.[43] Patient education to recognize the symptoms and signs of DKA, volume depletion, orthostatic hypotension, and genital mycotic infection is recommended,[101,102] and patients should be encouraged to maintain sufficient hydration and carbohydrate intake.[103]

Conclusions

With the rising burden of CKD and related complications in the Philippines, management strategies with newer treatment options are warranted. Globally, SGLT2 inhibitors have shown renoprotective benefits in patients with CKD, with and without T2D. Large clinical outcome trials support the beneficial renal effects of SGLT2 inhibitor treatment across a range of eGFR levels and albuminuria with tolerable safety. Several international guidelines also recommend initiating SGLT2 inhibitors in patients with stage 3 or higher CKD, irrespective of T2D status. Considering the efficacy and safety

profile, SGLT2 inhibitors should be routinely prescribed in this patient population in Philippines to reduce progression of CKD. There is also an urgent need to incorporate SGLT2 inhibitors in local guidelines in Philippines to enable appropriate patient selection for use of SGLT2 inhibitors in routine clinical practice in the Philippines.

Data Sharing Statement

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable formal request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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