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REVIEW

Clinical Evaluation of Dapagliflozin in the Management of CKD: Focus on Patient Selection and Clinical Perspectives

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Abstract: Dapagliflozin is a selective sodium–glucose cotransporter 2 (SGLT2) inhibitor that was recently approved in the USA and the EU for the treatment of adults with chronic kidney disease (CKD) with or without diabetes mellitus (DM). The DAPA-CKD trial showed a 39% decline in the risk of worsening kidney function, onset of end-stage kidney disease, or kidney failure-related death. Patients with lower levels of eGFR and higher levels of albuminuria are among those who stand to gain the greatest absolute benefits. These benefits were similar in both patients with or without diabetes, thus undermining the hypothesis that these drugs mitigate glycemia-related nephrotoxicity. Suggested mechanisms for renal protection include hemodynamic effects; BP reduction and improving salt sensitivities and metabolic effects; and glucose, uric acid and triglycerides (TG)-lowering effects. There have been already many excellent reviews on dapagliflozin and CKD management. Most of them cover both efficacy and safety. This review will focus on clinical perspectives and patient selection for the practicing clinician.

Keywords: dapagliflozin, SGLT 2inhibitors, CKD, proteinuria

Introduction

Chronic Kidney Disease Management and the Evolution of SGLT-s Inhibitors

The Kidney Disease: Improving Global Outcomes (KDIGO) working group defines Chronic Kidney Disease (CKD) as abnormalities of kidney structure or function present for >3 months, with implications for health. The KDIGO CKD risk score is classified based on estimated glomerular filtration rate (eGFR) and albuminuria (Figure 1).[1] Diabetes and hypertension remain the leading causes of CKD in the United States and worldwide.[1]

CKD affects 12% of the global population and is a major cause of morbidity and mortality consuming a significant proportion of the health-care resources.[2,3] According to the United States Center for Disease Control and Prevention (CDC), 1 in 7 (15%) US adults or a total of 37 million people are estimated to have CKD. Globally, the prevalence of CKD is estimated at 9.1% (697.5 million cases)[4] CKD increases the risk for all-cause mortality, cardiovascular mortality, kidney failure, and other adverse outcomes. In 2018, treating Medicare beneficiaries with CKD cost over $81.8 billion, and treating people with end-stage kidney disease (ESKD) cost and additional $36.6 billion.[3]

Often times, CKD is referred to as the "silent killer" considering that as many as 9 in 10 adults with CKD do not know they have CKD. Global estimates indicate that 1.2 million deaths were attributable to chronic kidney disease in 2017. Additionally, about 2 in 5 adults with severe CKD do not know they have the disease, leading to delayed diagnosis and delivery of care.[3,5]

There is no cure for CKD and for decades, management has been focused on delaying its progression and preventing cardiovascular complications. Treatment options have been limited to blood pressure control, reduction of albuminuria and optimization of glycemic control. Clinicians have a few tools to achieve these treatment targets. Guidelines recommend reducing blood pressure to a target of 130/80 mm Hg in most CKD patients. Screening for proteinuria is

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories Description and range		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73m²) Description and range	G1	Normal or high ≥90			
	G2	Mildly decreased 60-89			
	G3a	Mildly to moderately decreased 45-59			
	G3b	Moderately to severely decreased 30-44			
	G4	Severely decreased 15-29			
	G5	Kidney failure <15			

Figure 1 KDIGO CKD staging by GFR and albuminuria categories.
Notes: Reprinted from *Kidney Int Suppl*, 3(1), Levin A, Stevens PE, Bilous RW, et al. Kidney Disease: Improving Global Outcomes CKD Working Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, 1–150, Copyright (2013), with permission from Elsevier.[1]

recommended at the time of diagnosis and at least once a year thereafter. Random measurement of urinary albumin and urinary creatinine is the method of choice.[1]

For almost 20 years, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were the cornerstone of CKD progression retardation strategies. However, neither class reduced the risk of all-cause mortality in patients with CKD and evidence for their use in patients with CKD without T2D is relatively limited. Results from two landmark clinical trials: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT), have shown a reduction in CKD progression in diabetic patients by 16–20% compared to placebo and calcium channel blockers.[6,7] Although renin angiotensin aldosterone blocking drugs reduce the risk of adverse renal outcomes in patients with diabetes, the risk remains high and there is a large need for new treatments that lower the risk of kidney failure and improve cardiovascular risks independent of BP control.[8] Furthermore, despite the above evidence of the benefits of renin aldosterone angiotensin system (RAAS) blockade, a large proportion of patients who meet the criteria for this treatment do not initiate it within 1 year of CKD diagnosis, highlighting a need for new therapies that can slow the progression of CKD.[9]

The Advent of SGLT-2 Inhibitors

Many years of research dedicated to understanding the role the kidneys play in handling glucose have led to the discovery of sodium-glucose co-transporters (SGLT). Currently, six different isoforms of SGLT cotransporters have been identified. However, SGLT-1 and 2 have been studied the most due to their role in glucose and sodium transport across the brush border of intestines and kidney cells.[10] SGLT2 is a transport protein responsible for the reabsorption of approximately 90% of filtered glucose, with the remainder being absorbed by another transporter protein, sodium-glucose co-transporter 1 (SGLT1). The development of inhibitors targeting SGLT began with experiments around the compound phlorizin, first isolated over 150 years ago by French chemists from the root bark and the apple tree.[11] In 1975, DeFronzo et al showed that phlorizin infusion in dogs increased fractional excretion of glucose by 60%, improving blood glucose levels without affecting the glomerular filtration rate and renal plasma flow. Despite these encouraging results, the use of phlorizins in the treatment of

diabetes mellitus was not pursued due to their poor bioavailability and their interference with glucose transport in other parts of the body.[12] It was not until 1995, when researchers found that phlorizin inhibited both SGLT1 and SGLT2 that revealed the phlorizin's side effects as SGLT1 is found in many tissues and plays a key role in absorbing glucose in the intestine. Subsequent research focused on phlorizins more selective to SGLT2 led to their approval for the treatment of diabetes mellitus type 2 by the European Medicines Agency in 2012. In the US, the first SGLT2 inhibitor to be FDA-approved was canagliflozin (marketed as Invokana®) in March 2013, followed by the approval of dapagliflozin (marketed as Farxiga®) in January 2014 and empagliflozin (marketed as Jardiance®) in August 2014. Ertugliflozin (Steglatro®) was approved in 2017. A fifth SGLT2i, sotagliflozin (Zynquista) is being developed.[13]

SGLT2 inhibitors have a unique mechanism of action independent of insulin or insulin sensitivity resulting from inhibition of SGLT2 in the proximal tubule of the kidney and allowing for their use in combination with other hypoglycemic agents including insulin. Inhibition of SGLT2 results in decreased renal glucose reabsorption by approximately 50% and therefore modestly lower elevated blood glucose levels and glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes. Along, they do not usually cause hypoglycemia. SGLT2 inhibitors also have a modest natriuretic effect that may lower blood pressure; however, this effect is typically transient due to other compensatory mechanisms. The blood pressure-lowering effect of SGLT2 inhibitors is likely influenced by several other effects of SGLT2 inhibition, including weight loss and diuresis.[14]

In 2008, the FDA antidiabetic drug guidance required cardiovascular outcome trials (CVOTs) for novel anti-diabetic medications to ensure that they do not increase the risk of myocardial infarction, stroke or cardiac death. Three SGLT2is (canagliflozin, empagliflozin, dapagliflozin) have been studied in cardiovascular outcomes trials; canagliflozin has also been studied in an additional randomized clinical trial involving patients with diabetic kidney disease. These studies revealed improved cardiovascular and renal outcomes which sparked interest in studying the cardio-renal protective effects of these agents.[15]

Table 1 summarizes the safety studies for the approved SGLT2 inhibitors available in the US.

Table 1 Summary of Trials on SGLT2 Inhibitors with Kidney Outcomes

Trial	CREDENCE (n = 4401)	CANVAS Program (n = 10,142)	EMPA-REG OUTCOME (n = 7020)	DECLARE-TIMI 58 (n = 17,160)	DAPA-CKD (n = 4304)
Inclusion criteria	eGFR 30 to <90 mL/min/1.73 m²; UACR >300–5000 mg/g	eGFR ≥30 mL/min/1.73 m²	eGFR ≥ 30 mL/min/1.73 m²	CLcr ≥60 mL/min	eGFR 25–75 mL/min/1.73 m²; UACR 200–5000 mg/g
Drug	Canagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Dapagliflozin
Median follow-up	2.6 yr	2.4 yr	3.1 yr	4.2 yr	2.4 yr
Outcomes: RR or HR Comparing SGLT2i with Placebo					
Dialysis, Txp, or death from kidney disease	0.72 (0.54–0.97)	0.56 (0.23–1.32)	0.90 (0.30–2.67)	0.42 (0.20–0.87)	NA
Dialysis, Txp, or sustained eGFR <15 mL/min/1.73 m²,d	0.68 (0.54–0.86)	0.77 (0.30–1.97)	0.60 (0.18–1.98)	0.31 (0.13–0.79)	0.64 (0.50–0.82)
Loss of kidney function; dialysis, Txp, or sustained eGFR <15 mL/min/1.73 m²,d; or death from kidney disease	0.66 (0.53–0.81)	0.53 (0.33–0.84)	0.54 (0.40–0.75)	0.53 (0.43–0.66)	0.56 (0.45–0.68)

Abbreviations: eGFR, estimated glomerular filtration rate; CLcr, creatinine clearance.

Mechanisms of Action

SGLT2 inhibitors inhibit sodium and glucose reabsorption in the proximal tubule, leading to increased sodium and chloride delivery to the macula densa. This results in vasoconstriction in the afferent arteriolar secondary to adenosine-mediated myogenic activation which leads to a reduction in the intra-glomerular pressure and glomerular filtration rate.

Based upon this physiologic action on the kidney, many pathways which lead to the cardiovascular and renal protective effects of SGLT-2 inhibition are triggered and these include natriuresis, reduced intra-glomerular pressure, tubule-glomerular feedback, blood pressure lowering, and reduced oxidative stress and fibrosis.[16]

Figure 2 outlines the systemic effects and mechanisms of action for SGLT2 inhibitors.

Dapagliflozin in Diabetes Mellitus

Dapagliflozin is a potent and specific SGLT-2 inhibitor and hence it increases the amount of glucose excreted in the urine and improves both fasting and post-prandial plasma glucose levels in patients with T2D.[17] The glucosuric effect of dapagliflozin results in caloric loss and a modest reduction in bodyweight, as well as mild osmotic diuresis and transient natriuresis.[18] These benefits have been demonstrated by multiple randomized controlled trials.[19]

The glucose-lowering effect of dapagliflozin was similar in patients with or without cardiovascular disease and hypertension.[20,21] In a pooled analysis of five, Phase 2–3 clinical trials of ≤52 weeks' duration, patients with T2D and a history of heart failure saw an improvement in glycated hemoglobin from baseline (placebo-adjusted mean change −0.55%; baseline 8.2%), bodyweight (−2.7 kg; baseline ≈97 kg) and systolic blood pressure (−2.1 mmHg; baseline ≈134
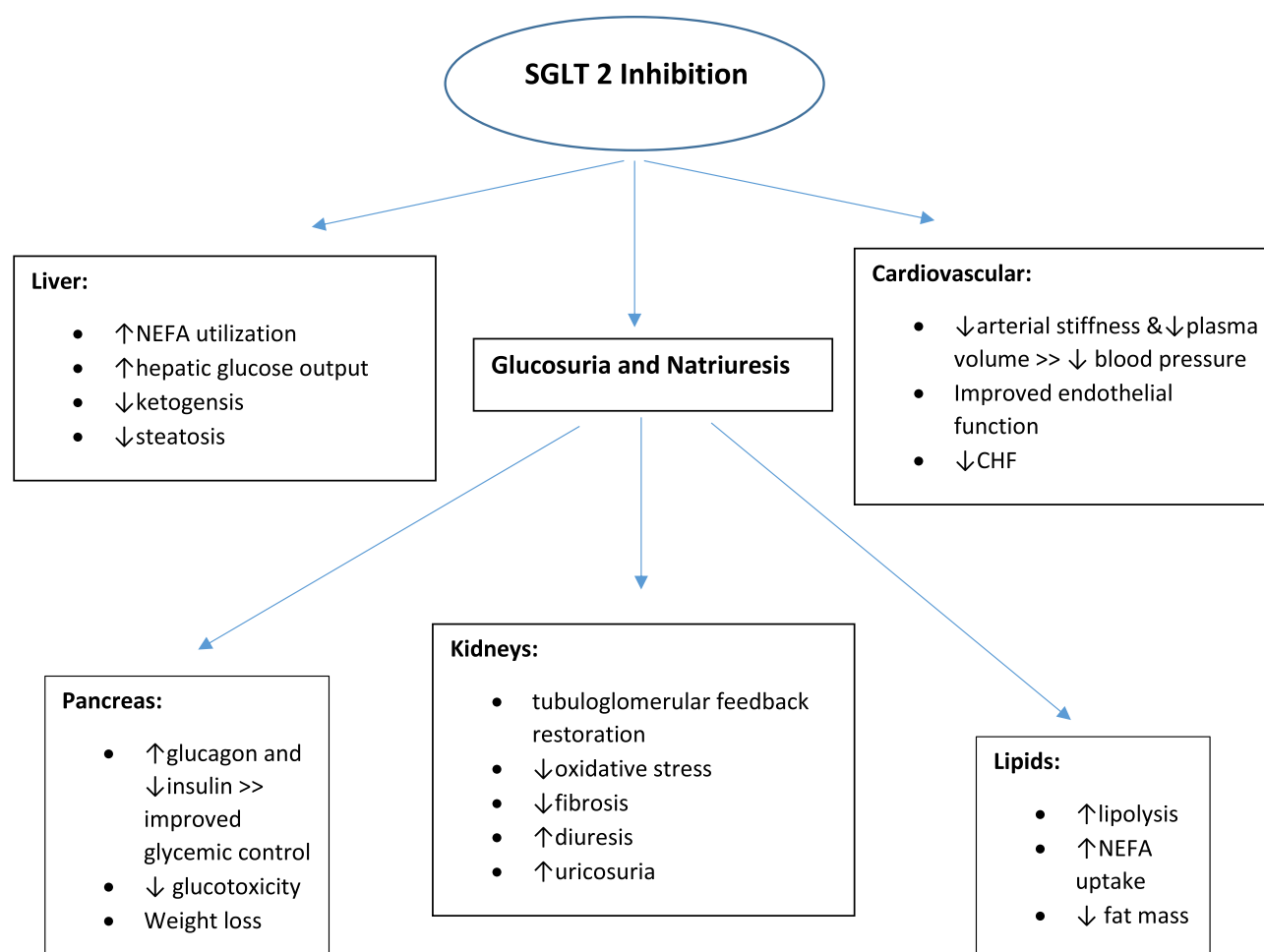

Figure 2 Mechanisms of action of SGLT2 inhibitors.

mmHg) with dapagliflozin 10 mg monotherapy or add-on therapy to other glycemic agents (n = 171) relative to placebo/active comparator (n = 149).[22]

Effect on Blood Pressure

Dapagliflozin achieves modest decrease in blood pressure. This effect may be explained by the diuretic and natriuretic properties of the drug which cause a decrease in circulating volume.[23] That being said, in two mechanistic studies, DAPASALT and DIAMOND, designed to study the effect of dapagliflozin in patients with CKD without T2D, it was demonstrated that during strictly controlled sodium intake, dapagliflozin increased glucosuria but not natriuresis or diuresis. This is probably related to compensatory mechanisms in the kidney that are activated during SGLT2 inhibition which may attenuate the natriuretic/osmotic-induced diuresis.[24] This brings up the question, how can we still have blood pressure reduction if there is no increase in natriuresis? Experts explain this by the positive effects of SGLT-2 inhibition on endothelial function, arterial stiffness and pulse wave velocity.[25]

In two Phase 3 studies, 10 mg once daily of dapagliflozin reduced SBP and improved glycemic control in patients with inadequately controlled type 2 diabetes and hypertension despite their receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy alone or in combination with one other antihypertensive.[24,25] SBP reduction was greater when dapagliflozin was added to a β blocker or a calcium-channel blocker when compared to a thiazide diuretic.[27]

Dapagliflozin in Heart Failure

The cardiovascular (CV) benefits of dapagliflozin were first observed in the DECLARE-TIMI 58 trial, in which dapagliflozin 10 mg/day significantly reduced the risk of CV death or HF hospitalization in patients with T2D who had or were at risk for atherosclerotic CV disease.[26] In the subsequent DAPA-HF trial, dapagliflozin 10 mg/day in addition to standard of care was associated with a significantly lower risk of worsening HF or CV death compared with placebo in patients with established heart failure, regardless of the presence or absence of T2DM. The benefits of Dapagliflozin also remained consistent regardless of background HF therapies.[29]

Dapagliflozin and Kidney Disease

We will review here the three major studies that examined dapagliflozin use in patients with chronic kidney disease. Inclusion criteria and patient characteristics in these trials are summarized in Table 2.

The DERIVE study (Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A), was a double-blind, multinational, phase 3 that evaluated the efficacy and safety of dapagliflozin in patients with type 2 diabetes and chronic kidney disease stage 3A. Patients with T2D and glycated hemoglobin of 7–11% and a BMI of 18–45 kg/m^2 were receiving other glucose-lowering regimens and had CKD stage 3A were randomized to receive 24 weeks of dapagliflozin 10 mg once daily (n = 159) or placebo (n = 161). At week 24, dapagliflozin significantly ($p = 0.05$) lowered HbA$_{1c}$ (primary endpoint; placebo-adjusted mean change −0.34; baseline ≈8.2%), fasting blood glucose (−0.9 mmol/L; baseline ≈10 mmol/L), bodyweight (−1.3 kg; baseline ≈90 kg) and SBP (−3.1 mmHg; baseline ≈135 mmHg) relative to placebo.[30]

The DECLARE-TIMI 58 trial, a randomized, double-blind phase 3 study, was designed to assess the effects of dapagliflozin on CV and renal outcomes. This study initially excluded patients with CKD, however results from the 2015 EMPA-REG OUTCOME study began to show decreased risk of incident or worsening kidney disease, progression to macroalbuminuria, and doubling of serum creatinine in patients treated with empagliflozin. Similarly, the 2019 CREDENCE trial found that canagliflozin reduced the risk of several cardiovascular and renal outcomes. The DECLARE-TIMI trial subsequently began to include patients with CKD. The study's two pre-specified secondary endpoints were renal composite outcome and death from any cause. At baseline, patients (n = 17,160 randomized) had a mean age of 64 years and 41% had established ASCVD, including coronary artery disease (33% of the patients) and heart failure (HF; 10%).[25] The mean duration of diabetes was ≈11 years, mean HbA1c was 8.3% and the mean estimated glomerular filtration rate (eGFR) was 85 mL/min/1.73 m^2 (45% and 7% of the patients had an eGFR of 60–90 and <60 mL/min/1.73 m^2, respectively). Patients were randomized to receive dapagliflozin 10 mg once daily or placebo

Table 2 Patients Characteristics in Dapagliflozin Studies

Trial	DERIVE	DECLARE-TIMI 58 (n = 17,160)	DAPA-CKD (n = 4304)	DAPA-HF (n=4744)
Inclusion criteria	GFR>45 mL/min/ 1.73 m^2	CLcr ≥ 60 mL/min	eGFR 25–75 mL/min/1.73 m^2; UACR 200–5000 mg/g	eGFR ≥ 30 mL/min/ 1.73 m^2
Median follow-up, months	24	50.2	28.8	18
Baseline ACEI or ARB use	132 (82.0%)	13,950 (81%)	1354 (31%)[a]; 2870 (67%)[b]	1332(56.1%)[a] 675 (28.4%)[b] 250 (10.5%)[c]
eGFR, mL/min/1.73 m^2				
≥90	Mean 53.6 (10.6)	8162 (48%)	0 (0)	Mean 66±19.6
60 to <90		7732 (45%)	454 (11%)	
45 to <60		1265 (7%)	1328 (31%)	
30 to <45		NA	1898 (44%)	
		0 (0)	624 (14%)	
Missing		1 (<0.1%)	0 (0)	
UACR, mg/g				
	Mean 29.0 (3.8–8474.0)	11,644 (68%)	NAc	Not reported
30–300		4030 (24%)	NA	
c		1169 (7%)	NA	

Notes: [a]Patients receiving ACEI. [b]Patients receiving ARB. [c]Patients receiving sacubitril/valsartan.
Abbreviations: GFR, glomerular filtration rate; CLcr, creatinine clearance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; UACR, urine albumin-to-creatinine ratio.

in addition to other glucose-lowering agents at the discretion of the treating physician. The median follow-up duration was 4.2 years (69,547 patient-years). dapagliflozin significantly lowered the rate of CV death/HHF versus placebo, but there was no significant between-group difference in the rate of major adverse cardiovascular events. Secondary analysis results suggested that dapagliflozin decreases the likelihood of progression of renal disease compared with placebo. The reduction in sustained decline in eGFR was ≥40% to <60 mL/min per 1.73 m^2 [hazard ratio (HR) 0.54; 95% CI 0.43–0.67; p < 0.0001), end-stage kidney disease (ESKD; HR 0.31; 95% CI 0.13–0.79; p = 0.013), and renal death or ESKD (HR 0.41; 95% CI 0.20–0.82; p = 0.012). The mean decrease from baseline in eGFR was significantly (*p* < 0.0001) greater with dapagliflozin than placebo at 6 months, but had equalized with placebo by 2 years, and was significantly (*p* < 0.0001) less than placebo by 3 and 4 years after randomization.[28,31]

The DECLARE-TIMI 58, EMPA-REG OUTCOME and CREDENCE only included patients with diabetes, and whether this benefit would extend to for adults without T2DM was unclear at that point. This formed the question of whether dapagliflozin would affect the progression of chronic kidney disease and cardiovascular death in patients with or without type 2 diabetes and chronic kidney disease characterized by eGFR reduction and microalbuminuria. The Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study, a multicenter, double-blind, randomized, placebo controlled study, was designed to answer this question. The study included 4304 participants with CKD (defined by eGFR of 25–75 mL/min/1.73 m^2 and albuminuria with albumin-to-creatinine ratio (ACR) of 200–5000 mg/g) with and without T2DM and compared the effect of dapagliflozin to placebo. At least a third of patients without diabetes saw changes associated with ischemic and hypertensive nephropathy, and had chronic glomerulonephritis (especially IgA nephropathy). The study was stopped early after

an interim safety analysis found conclusive evidence of the benefit of Dapagliflozin, which demonstrated to reduce the composite endpoint of decline of ≥50% in eGFR, new ESKD, renal mortality, or CVD mortality (9.2% vs 14.5%; HR 0.61; 95% CI 0.51–0.72; NNT=19). Remarkably, this benefit was similar regardless of T2D status. The medication was also associated with reduction in other endpoints, including all-cause mortality (4.7% vs 6.8%; 0.69; 0.53–0.88; NNT=48). There was a slightly higher risk of major hypoglycemia (0.7% vs 1.3%; P=0.04; NNH=166) with dapagliflozin use.

The study concludes that among patients with chronic kidney disease stages 2 through 4 and elevated levels of albuminuria, regardless of the presence or absence of diabetes, the risk of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lowered (39%) when dapagliflozin is used in combination with standard of care treatment with RAAS blockade compared to placebo. The absolute risk reduction was 5.3% over a median time of 2.4 years, dapagliflozin also reduced the relative risk of death from any cause by 31% compared to placebo.[32] The trial was unique in that one-third of patients did not have diabetes, and yet these benefits were the same regardless of diabetes status. This finding contradicts the hypothesis that such drugs mitigate glycemia-related nephrotoxicity.

The findings in the DAPA-CKD trial led the US Food and Drug Administration in April 2021 to approve dapagliflozin as the first drug that reduces the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression regardless of diabetes status.[33]

The DAPA-CKD results were followed by two sub-analyses. The first aimed to answer the question: is dapagliflozin safe in CKD stage 4 patients? Glenn M. Chertow et al analyzed data of 624 of 4304 (14%) patients in the DAPA-CKD study who had stage 4 CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2). Compared with placebo, dapagliflozin was associated with a significant 27% improvement in the primary composite endpoint time of 50% or more decline in eGFR as well as end-stage kidney disease, or kidney or cardiovascular death in patients with advanced CKD. Furthermore, dapagliflozin significantly lowered both the risks for the kidney and cardiovascular endpoints by 29% and 17%, respectively, and the risk for all-cause mortality by 32%. Compared to placebo, dapagliflozin was superior at preservation of kidney function, with eGFR decreasing by 2.15 vs 3.38 mL/min/1.73 m^2 per year. Rates of serious adverse events including major hypoglycemia, bone fractures, kidney-related events, and amputation were similar between the two groups. It was concluded that the effects of dapagliflozin among patients with stage 4 CKD are similar to those patients with mild-to-moderate CKD.[34] It should be noted that the lower number of participants with eGFR <30 mL/min/1.73 m^2 and the different underlying diseases may have caused a certain bias.

Another pre-specified subgroup analysis was performed to determine whether these outcomes were influenced by the presence or absence of cardiovascular disease. Of the total study population, 37.4% were secondary prevention patients, this group was predominantly males and likely to have diabetes. Additionally, the secondary prevention group had a higher BMI and blood pressure versus other participants. The primary and secondary prevention groups had similar eGFR and median urinary albumin-to-creatinine ratio. Rate of kidney failure was similar between the two groups, but the secondary prevention group had higher rates of adverse cardiovascular outcomes. The primary composite outcome (which included a sustained decline in eGFR of 50% or lower, end-stage kidney disease, and kidney or cardiovascular death) was significantly reduced by dapagliflozin treatment in both the primary and secondary prevention groups. Additionally, dapagliflozin treatment yielded similar reductions in terms of composite outcome of heart failure hospitalization, cardiovascular death, and all-cause mortality. No differences in rates of adverse events were detected between the groups. Based on these data, it was concluded that benefits from dapagliflozin are present in patients with and without cardiovascular disease.[35]

Another interesting sub-analysis examined the efficacy and safety of dapagliflozin in patients with immunoglobulin A nephropathy (IgAN). Of 270 participants with IgAN (254 [94%] confirmed by previous kidney biopsy), 137 were randomized to dapagliflozin and 133 to placebo. Mean age was 51.2 years; mean eGFR, 43.8 mL/min/1.73 m^2; and median urinary albumin-to-creatinine ratio, 900 mg/g. Median follow-up was 2.1 years. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/min/1.73 m^2/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo. Adverse events leading to study

drug discontinuation were similar with dapagliflozin and placebo. There were fewer adverse events with dapagliflozin, and no new safety findings in this population. The analysis concluded that dapagliflozin reduces the risk of chronic kidney disease progression in participants with IgAN and has a favorable safety profile.[36]

Given the diversity of CKD etiologies in this study's patients population, the results can be generalized to a wide spectrum of patients with CKD in clinical practice. Dual renin-angiotensin/SGLT2 inhibition may become the new standard. The same rule applies for patients with podocytopathy-related focal segmental glomerulosclerosis lesions. Experts believe that from now on, IgAN and podocytopathy trials without SGLT2 inhibition as background therapy and without glomerular filtration rate decline as a primary outcome criterion will be of limited value.[37]

It should be noted, however, that patients with type 1 diabetes, polycystic kidney disease, and recent immune disorders were not included in this trial. Furthermore, African American patients were poorly represented in most of the SGLT2 inhibitor studies including DAPA-CKD (4.4%), while 34% of the participants in the DAPA-CKD trial were Asian.[38]

Another limitation of the DAPA-CKD is that CKD patients without proteinuria (albuminuria <200 mg/g) were excluded; therefore, benefits in this patients' group remain unknown.[39]

Dapagliflozin versus Other SGLT2 Inhibitors

Data from many large cardiovascular outcome trials in patients with diabetes (EMPA-REG, CANVAS, DECLARE-TIMI 58, and VERTIS CV) as well as heart failure (DAPA-HF1 and EMPEROR-Reduced2) have demonstrated consistent renal benefits from SGLT2 inhibitors including preservation of estimated glomerular filtration rate (eGFR) and reduced rates of renal outcomes. The CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), published in 2019, showed that in patients with T2D and urine albumin-to-creatinine ratio (UACR) of 300–5000 mg/g and eGFR of 30–90 mL/min/1.73 m^2 100 mg/day, 100 mg/day of canagliflozin reduces the risk of the composite endpoint of end-stage kidney disease, doubling of serum creatinine from baseline, and death from renal or cardiovascular disease when compared to placebo (HR 0.70; 95% CI 0.59–0.82; p = 0.00001). Results from CREDENCE promoted a new KDIGO guideline of a class 1a recommendation that patients with type 2 diabetes and CKD with eGFR >30 mL/min/1.73 m^2 be treated with an SGLT2 inhibitor.[40]

Similar changes in sCr and GFR were observed in both DAPA-CKD and CREDENCE compared to placebo. In the DAPA-CKD trial, dapagliflozin reduced the primary endpoint by 39%, resulting in a number needed to treat of 19. In CREDENCE, primary composite endpoints were reduced by 30%. However, DAPA-CKD cohort included patients with CKD without diabetes (32% of patients) and with more advanced kidney disease and less cardiac disease than the one enrolled in CREDENCE. The rate of heart failure was 10.9% and the rate of CVD was 37% at baseline in DAPA-CKD compared with 14.9% and 50.5% in CREDENCE.[13,40]

The EMPA-KIDNEY trial included patients with or without diabetes with eGFR 20–45 mL/min/1.73 m^2 regardless of albuminuria or eGFR 45–90 mL/min per 1.73 m^2 with UACR ≥200 mg/g on maximally tolerated RAAS blockade. A total of 6609 patients with a mean eGFR of 37.5 mL/min per 1.73 m^2 were enrolled in this study. 48% of the participants had a UACR <300 mg/g. The primary outcome of this trial was a sustained ≥40% decline in eGFR, ESKD, or death from renal or cardiovascular causes. The EMPA-KIDNEY trial was stopped early in March 2022 for efficacy suggesting that CKD patients without albuminuria also benefit from SGLT2 inhibitors. The results are not published at the time of writing this manuscript.[41]

The choice of SGLT-2 inhibitor should be based upon the current FDA indication, the patient's kidney function at time of initiation as well as affordability.

Table 3 compares different SGLT-2 inhibitors by indication.

Pharmacology/Pharmacodynamics Properties of Dapagliflozin

Dapagliflozin is rapidly absorbed following oral administration, with peak plasma concentrations usually achieved at 2 hours. Dapagliflozin pharmacokinetics are not affected by food. After a 10 mg dose, the absolute oral bioavailability of dapagliflozin is 78%. The mean steady-state volume of distribution of dapagliflozin is 118 L and it is ≈91% protein bound. The mean half-life is 12.9 hrs. Dapagliflozin is largely metabolized in the liver via CYP to an inactive metabolite

Table 3 SGLT-s Inhibitors Dosing and Indications

SGLT-2 Inhibitors Available in the United States	Dapagliflozin	Canagliflozin	Empagliflozin	Ertugliflozin
Doses	5–10 mg daily	100–300 mg daily	10–25 mg daily	5–15 mg daily
Renal dosing	eGFR >25 mL/min/1.73 m^2, 5–10 mg daily with no dose adjustment. eGFR <25 mL/min/1.73 m^2, initiation is not recommended but use is to be continued till need for kidney replacement therapy	eGFR >60 mL/min/1.73 m^2, 300 mg daily. eGFR 30–59 mL/min/1.73 m^2, 100 mg daily eGFR <30 mL/min/1.73 m^2, initiation is not recommened but use at 100 mg daily can be continued	eGFR <45 mL/min/1.73 m^2, avoid use	eGFR <30 mL/min/1.73 m^2, avoid use
Indications based on evidence				
Diabetes Mellitus	Improves glycemic control	Improves glycemic control	Improves glycemic control	Improves glycemic control
Renal outcomes	Reduce the risk of kidney disease progression in patients with CKD with and without diabetes	Reduce the risk of end stage kidney disease and doubling of serum creatinine in adults with type 2 diabetes mellitus and diabetic nephropathy and albuminuria		
Cardiovascular outcomes	Reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease. Reduce the risk of cardiovascular death and hospitalization for heart failure in adult patient with heart failure and reduced systolic ejection fraction	Reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. Reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria	Reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.	

(dapagliflozin 3-*O*-glucuronide). The drug and its metabolites are mainly excreted in the urine, with 75% of a dose recovered in the urine and 21% in the feces.[39]

Table 4 summarizes the drug characteristics.

Adverse Effects
Genital Infections
Genital contamination leading to vulvovaginitis and balanitis is considered the most common adverse reaction to dapagliflozin. In clinical trials of SGLT-2 inhibitors, there was a two- to fourfold increase (10–15% of women) in the incidence of vulvovaginal candidiasis. Results from twelve studies which included patients treated with dapagliflozin at a dose of 5mg, 10 mg and placebo, showed an infection rate of 5.7%, 4.8% and 0.9%, respectively.[42,43] Patients should be cautioned when prescribing dapagliflozin regarding the possibility of genital infections. Dapagliflozin should be stopped in the case of recurrent or relapsing infections.

Table 4 Dapagliflozin Drug Characteristics

Features and Properties of Dapagliflozin	
Indications	
• Chronic kidney disease stages 1–4 (eGFR >25 mL/min/1.73 m^2) with proteinuria (>200 mg/g) • Diabetes mellitus type II • Congestive heart failure	
Mechanism of Action	
Selective sodium–glucose cotransporter 2	
Dosage and administration	
5–10 mg oral tablets once a day	
Pharmacokinetic Profile	
Bioavailability	78%
Mean half-life	12.9 hours
Volume of distribution	118 L
Excretion	75% urine and 21% feces
Contraindications	
• Diabetes mellitus type 1 • Advanced CKD with eGFR <25 mL/min/1.73m^2 (patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and HF) • Prior diabetic ketoacidosis (DKA)	
Side effects	
• Genital yeast infections (vaginal and penile) and UTIs • Runny nose and sore throat • Changes in urination, urgency, nocturia and increased urine output. • Dehydration	
Practical consideration when initiating therapy with dapagliflozin including patient education	
• Ensure euvolemia and consider decreasing the dose of diuretics by 25–50% • Assess risk of hypoglycemia and the need to decrease the dose of other hypoglycemic agents or insulin therapy • Counsel the patient on "sick days" or "procedure day" • Educate the patient about foot care • Educate patient about symptoms of UTI and genital yeast infections. Assess kidney function in 1 month in selected high risk patients at risk of AKI	

Urinary Tract Infections

In clinical trials, SGLT2 inhibitors increased the rate of urinary tract infections (8.8 versus 6.1%) There was a higher risk of emergent infections in those having previous history. Patients administered with dapagliflozin of 5mg, 10mg and placebo developed infection at rates of 5.7%, 4.3% and 3.7%, respectively. There are also reports of severe urosepsis and pyelonephritis with SGLT-s inhibitors' use.[14,44]

A report in the annals of medicine outlined 55 unique case reports to the FDA of Fournier's gangrene (FG) in patients receiving SGLT2 inhibitors between March 2013 and January 2019. The patients ranged in age from 33 to 87 years; 39 were men, and 16 were women. Time to onset after initiation of SGLT2-inhibitor therapy ranged from 5 days to 49 months. All patients had surgical debridement and were severely ill. Reported complications included diabetic ketoacidosis (n = 8), sepsis or septic shock (n = 9), and acute kidney injury (n = 4). Eight patients had fecal diversion surgery, 2 patients developed

necrotizing fasciitis of a lower extremity that required amputation, and 1 patient required a lower-extremity bypass procedure because of gangrenous toes. Three patients died. For comparison, the FDA identified 19 FG cases associated with other antidiabetic agents between 1984 and 2019: metformin (n = 8), insulin glargine (n = 6), short-acting insulin (n = 2), sitagliptin plus metformin (n = 2), and dulaglutide (n = 1). These patients ranged in age from 42 to 79 years; 12 were men, and 7 were women. Two patients died.[45,46]

Four cases of FG attributed to the use of dapagliflozin specifically were published recently. Obesity and elevated levels of hemoglobin A1C were common patient characteristics in these cases. All patients were required to stay in the intensive care unit and underwent surgical intervention. The underlying mechanism is unclear; however, elevated blood glucose levels coupled with glucosuria caused by SGLT2 in patients with impaired microvascular supply and decreased immune response provide a favorable setup for urinary infections.

Further studies are needed to determine risk factors and to generate evidence for a causal connection between dapagliflozin and FG. In the meantime, it is advised to counsel patients about the low risk of FG though not a negligible one especially in patients who are obese and have poorly controlled diabetes mellitus.[47]

While history of UTIs does not preclude the use of dapagliflozin, patients should be forewarned about the increased risk, and the drug should be stopped in the case of recurrent or relapsing infections.

Bladder Cancer

In dapagliflozin clinical trials, there were 10 cases of bladder cancers. Five patients were diagnosed in the first 6 months of its use, a time period which is too limited to reliably indicate whether dapagliflozin is carcinogenic, but this finding certainly signals a risk. The FDA recommended post-marketing surveillance studies.[48]

A pooled analysis of 21 clinical trials has suggested that dapagliflozin is not linked to increased risk for bladder cancer. A total of 9/5936 dapagliflozin-treated patients versus 1/3403 otherwise-treated patients developed bladder cancer. All bladder cancer patients had clinical risk factors for the disease (>60 years of age, male patients, tobacco use and microscopic hematuria).[49]

A study is ongoing to compare the incidence of bladder and breast cancer among male and female patients with type 2 diabetes who are new users of dapagliflozin compared with those who are new users of antidiabetic agents in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.[50] Till the results become available, it is recommended to avoid dapagliflozin in patients at increased risk of bladder cancer or with a prior history of bladder cancer.

Hypoglycemia

Dapagliflozin is not linked with hypoglycemia. When dapagliflozin is added to other hypoglycemic agents such as insulin and sulfonylurea, the combination increases the risk for hypoglycemia. It is recommended that at the initiation of therapy, hypoglycemic risks can be minimized by reducing the dose of other agents.[51]

Hypotension

By inducing glucosuria, SGLT2 inhibitors can cause osmotic diuresis and intravascular volume contraction. This may be especially be important in older patients, or those taking diuretics, or RAAS blocking agents.[52]

Using data from the DAPA-HF trial, researchers examined the effects of baseline systolic blood pressure on 1205 patients with heart failure and reduced ejection fraction who were randomized to either treatment with dapagliflozin or placebo. The dapagliflozin group experienced superior outcomes versus the placebo group across the range of SBP in adjusted and unadjusted analyses. dapagliflozin was well-tolerated and associated with better outcomes compared with placebo in patients with HFrEF across the range of SBP. Only a small proportion of patients experienced a decline in SBP to below 90 mmHg and this proportion was similar in each treatment group (6.3% with dapagliflozin and 5.6% with placebo); the equivalent proportion with a SBP decreasing to <85 mmHg was even smaller and balanced between treatment groups (2.9% and 2.7%, respectively).[53]

Dehydration

Dapagliflozin-based therapy is not associated with severe dehydration, considered to be an uncommon effect.[54]

Acute Kidney Injury (AKI)

Based on post-marketing Food and Drug Administration Adverse Events Reporting System (FAERS) reports, in June 2016, the US Food and Drug Administration (FDA) issued a warning that SGLT2is (especially canagliflozin and dapagliflozin) might cause AKI.[55,56]

There have been 101 cases of possible SGLT2-associated acute kidney injury reported to the FDA. Some of these post-marketing reports were in patients taking dapagliflozin. Some of which required hospitalizations and dialysis. Approximately half of these cases occurred within 1 month of initiating the drug, and most patients improved after discontinuation. It is not known how many patients had an underlying chronic kidney disease. Some patients may have been volume depleted, hypotensive, or taking other medications that could affect the kidneys. In one case report, a biopsy was done that revealed acute tubular necrosis. The patient recovered after 4 weeks on hemodialysis.[57]

In a systematic review and meta-analysis of the effect of SGLT2is on renal adverse events (AEs) in randomized controlled trials and controlled observational studies, 30 trials identified 410 serious AEs due to AKI. SGLT2is reduced the odds of developing AKI by 36% (odds ratio [OR] 0.64 [95% confidence interval (CI) 0.53–0.78], $p < 0.001$). A total of 1089 AKI events of any severity (AEs and serious AEs [SAEs]) were published in 41 trials (OR 0.75 [95% CI 0.66–0.84], $p < 0.001$). This sweeping review concluded that SGLT2i reduced the odds of suffering AKI with and without hospitalization in randomized trials and the real-world setting, despite the fact that more AEs related to hypovolemia have been reported.[58]

It is important to note that SGLT2 inhibitors induce an acute, reversible reduction in GFR, which is often referred to as the GFR "dip." This response pattern suggests that these agents reduce glomerular hypertension, similar to what is seen with ACE inhibitors/ARBs' use. The clinical implications of an acute eGFR dip were previously unknown and led to concerns around the risk of AKI with these therapies. However, data from three recent analyses— Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV), and canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) are reassuring and confirm the dip in eGFR is not associated with progressive long-term kidney function loss or AKI.[59]

A few recent case reports of biopsy-proven osmotic nephropathy with SGLT2-inhibitors have been published. These five patients ranged in age from 41 to 66 years, and all had DM/hypertension and CKD with eGFR ranging from 27 to 79 mL/min/176 m^2. Three patients were on Dapagliflozin, 1 on canagliflozin and 1 patient on empagliflozin. Serum creatinine on presentation ranged from 1.1mg/dL to 10.7mg/dL (mean 4.6mg/dL). Kidney biopsy in all patients revealed findings consistent with osmotic nephropathy with vacuolization and cell swelling limited to the proximal tubules. With supportive care and SGLT2-inhibitor discontinuation, four patients recovered kidney function back to baseline and one patient left with higher stage CKD. Interestingly, osmotic nephropathy caused by phlorizin was described in 1935 by Homer Smith. The exact etiology of osmotic nephropathy caused by SGLT inhibitors is not entirely clear; however, a kidney biopsy may be warranted in patients with SGLT2 inhibitor–associated acute kidney injury that does not recover to baseline within 5–7 days.[60]

In the DAPA-CKD trial, the incidence of renal related adverse events (defined as doubling of serum Creatinine) between two subsequent study visits was 63 (2.9%) in the treatment group and 91 (4.2%) in the placebo group (hazard ratio 0.68 [95% confidence interval 0.49, 0.94]). Acute kidney injury–related serious adverse events were not significantly different between groups and occurred in 52 (2.5%) and 69 (3.2%) participants in the dapagliflozin and placebo groups, respectively (0.77 [0.54, 1.10]). This analysis suggests that dapagliflozin reduced the risk of abrupt declines in kidney function in patients with CKD and albuminuria.[61]

Nevertheless, renal function should be assessed prior to initiation of dapagliflozin and monitored during treatment. The drug should be used with caution in patients with comorbidities that might predispose to acute kidney injury (eg, heart failure, hypovolemia) and in conjunction with other medications that predispose to AKI (nonsteroidal anti-inflammatory drugs [NSAIDs], ACE inhibitors/ARBs, diuretics). Dose adjustments and more frequent monitoring are required in patients with moderate chronic kidney disease.

Diabetic Ketoacidosis (DKA) and Euglycemic DKA

SGLT2 inhibitors are thought to increase the risk of DKA. In a population-based cohort study from Canada and the United Kingdom, SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) compared with dipeptidyl peptidase 4 (DPP-4) inhibitors were associated with an increased risk of DKA (incidence 2.03 versus 0.75 per 1000 person-years [HR 2.85, 95% CI 1.99–4.08]). Among the three SGLT2 inhibitors, canagliflozin was associated with the highest risk.[62]

In several studies, "euglycemic" DKA (Eu-DKA) has been reported in patients with type 2 diabetes taking dapagliflozin. Eu-DKA is an uncommon form of DKA that is characterized by metabolic acidosis (pH <7.3), a decreased level of serum bicarbonate (<18 mEq/L), and a relatively low blood glucose level (<200 mg/dL).[63] In these individuals, the absence of substantial hyperglycemia delays recognition of the problem and makes diagnosis challenging.[64,65]

In one report, 33 articles on SGLT2 inhibitors-induced ketoacidosis in the context of surgical treatment were identified. According to this literature research, risk factors for the development are infection, perioperative fasting, surgical stress, and insulin dose reduction. This emphasizes the need to withhold treatment with SGLT-2 inhibitors for at least 24–48 h prior to surger.y[66] Similarly, patients should hold the drug for illness or excessive exercise or alcohol intake and seek medical help early.

In DAPA-CKD, 0/2149 receiving dapagliflozin developed DKA compared to 2/2149 (<0.1) in the placebo group.[32]

The proposed mechanisms of eu-DKA induced by SGLT-2 inhibitors are as follows: SGLT-2 inhibitors reduce blood glucose levels, thereby decreasing the secretion of endogenous insulin by pancreatic β-cells. This in turn stimulates pancreatic α-cells, leading to increased glucagon secretion. SGLT-2 inhibitors also directly stimulate α-cells, thereby increasing plasma glucagon concentration and promoting hepatic ketogenesis.[67]

The risk of SGLT2 inhibitors with regard to DKA has been demonstrated in placebo-controlled trials in type 1 diabetes. An increased risk for DKA was seen in these studies even though participants at high risk for DKA were excluded at baseline and substantial efforts to mitigate this risk were undertaken. SGLT2 inhibitors are not indicated in type 1 diabetes mellitus and off-label use in type 1 diabetes is discouraged.[67]

In practice, patients should be instructed to avoid ketogenic diet "carbohydrate-free" diet. We also recommend checking serum ketones in any patient with nausea, vomiting, or malaise while taking SGLT2 inhibitors, and SGLT2 inhibitors should be discontinued if acidosis is confirmed. In addition, clinicians should be mindful that acute illnesses such as diffuse paralytic ileus and urinary tract infection, as well as dietary restrictions or fasting in patients with DM, can all be considered potential predisposing factors for SGLT-2 inhibitor-associated eu-DKA. Therefore, we recommend withholding SGLT2 inhibitors in this setting.

Amputations

Compared with other oral and injectable diabetes agents, SGLT2 inhibitors, particularly canagliflozin, are associated with an increased risk of amputation.[68,69]

In two randomized trials evaluating canagliflozin versus placebo in patients with type 2 diabetes and established CVD, there was an approximately two-fold increased risk of lower limb amputations (mostly toe and midfoot) in patients taking canagliflozin. Patients with a history of prior amputation, peripheral vascular disease, and neuropathy were at highest risk for amputation.[70]

In another study of over eight million case safety reports, 79 lower-limb amputations associated with the use of SGLT2 inhibitors were reported since 2013. An increased risk of lower-limb amputations was reported with canagliflozin, empagliflozin, and dapagliflozin (PRRs 8.91, 6.86, and 2.62, respectively).[71]

The incidence of amputations (defined as cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma) was 35/2149 (1.6%) in the dapagliflozin group versus 39/2149 (1.8%) in the placebo group.[32]

In clinical practice, SGLT2 inhibitors should be avoided in patients at risk for foot amputation, including neuropathy, foot deformity, vascular disease, and history of previous foot ulceration. Patients taking SGLT2 inhibitors should be monitored for signs and symptoms of foot ulceration.

Bone Fracture

Some studies have shown an increase in the incidence of fractures in patients taking canagliflozin. These low trauma fractures were reported within 12 weeks following initiation of the drug. Orthostatic hypotension was thought to be the underlying cause of these incidents.

A meta-analysis of trials evaluating safety outcomes did not show an increased risk of fracture with dapagliflozin or empagliflozin. The increase in fracture with canagliflozin was not significant (odds ratio [OR] 1.15, 95% CI 0.71–1.88).[72] In addition, a total of 85/2149 (4.0) of patients treated with dapagliflozin in the DAPA-CKD study had fractures compared to 69/2149 (3.2) in those who received placebo.[32]

Patient Selection and Clinical Perspectives

Renal Indications

As stated above, several clinical trials provided clear and consistent data that SGLT2 inhibitors have marked renal benefits, with preservation of estimated glomerular filtration rate (eGFR) and reduced rates of renal outcomes observed with SGLT2 inhibitors compared with placebo in each of these trials. DAPA-CKD in particular created a paradigm shift in the management of chronic kidney disease (CKD). Current indications for dapagliflozin include chronic kidney disease stages 1–4 (eGFR>25 mL/min/1.73 m^2) with proteinuria (>200 mg/g): To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.[32] The 2020 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for management of diabetes and CKD aims to address this issue by providing new clinical recommendations and practical points for clinicians.[2] The guideline recommends treatment with SGLT2i for patients with type 2 diabetes, CKD, and eGFR >30 mL/min per 1.73 m^2 at any level of current glycemic control.[73]

Limitations of use: Dapagliflozin is not recommended in patients with type I diabetes, polycystic kidney disease, or in those who currently require or have a recent history of immunosuppressive therapy for kidney disease.

Figure 3 outlines the current approach to CKD with proteinuria and where dapagliflozin is indicated.

Contraindications

- Diabetes mellitus type 1
- Advanced CKD with eGFR <25 mL/min/1.73m^2 (patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and HF)
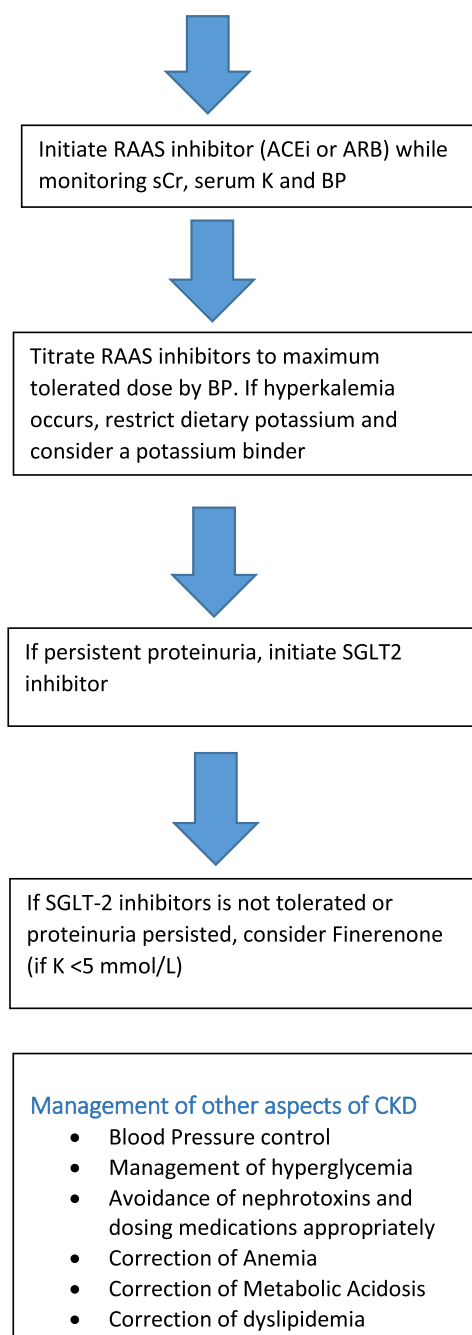- Prior diabetic ketoacidosis (DKA)

Precautions

- Frequent bacterial urinary tract infections or genitourinary yeast infections.
- In conjunction with NSAIDs, RAAS inhibitors, and diuretics.
- Peripheral vascular disease, foot ulceration, and neuropathy.
- Patients at high risk for Diabetic Ketoacidosis (DKA).
- Low bone mineral density and high risk for falls and fractures.
- Conditions that predispose to AKI, eg, liver disease and hypovolemia.
- Known history of bladder cancer or at risk of bladder cancer.
- Risk of hypovolemia, eg, ileostomy.
- SGLT-2 inhibitors should be withheld at least 24–48 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity and restarted only in stable clinical conditions.
- Patients with severe hepatic impairment were excluded from clinical trials and therefore we recommend avoiding using the drug in this population.

Prior to Initiating Dapagliflozin, Clinician Should

- Obtain a baseline kidney function (sCr, albuminuria/proteinuria) and liver function tests.
- Assess and correct hypovolemia as it is optimal to start therapy when the patient is euvolemic. Consider reducing the dose of diuretic therapy by 25–50% at the initiation of dapagliflozin.

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Management of Proteinuric CKD
(ACR > 300 mg/g or proteinuria >0.5 gr/day)

Initiate RAAS inhibitor (ACEi or ARB) while monitoring sCr, serum K and BP

Titrate RAAS inhibitors to maximum tolerated dose by BP. If hyperkalemia occurs, restrict dietary potassium and consider a potassium binder

If persistent proteinuria, initiate SGLT2 inhibitor

If SGLT-2 inhibitors is not tolerated or proteinuria persisted, consider Finerenone (if K <5 mmol/L)

Management of other aspects of CKD
- Blood Pressure control
- Management of hyperglycemia
- Avoidance of nephrotoxins and dosing medications appropriately
- Correction of Anemia
- Correction of Metabolic Acidosis
- Correction of dyslipidemia

Figure 3 Management of CKD with proteinuria.

- Decrease the dose of insulin and oral hypoglycemic agents to reduce the risk of hypoglycemia.

Dosing
Dose of 10 mg once daily can be taken any time of day with or without food.

For patients with reduced liver function, a starting dose of 5 mg is recommended.

In impaired renal function: if eGFR ≥45 mL/minute/1.73 m^2, no dosage adjustment is necessary.

In patients with eGFR 25 to <45 mL/minute/1.73 m^2, no dosage adjustment is necessary, but caution should be used.

In patients with eGFR <25 mL/minute/1.73 m^2, dapagliflozin should not be initiated; however, patients previously established on dapagliflozin may continue 10 mg once daily. This is consistent with the DAPA-CKD trials enrollment.[74]

Monitoring During Treatment

Clinicians should monitor the following during treatment with dapagliflozin:

- Fasting blood sugar and glycated hemoglobin
- Renal function (BUN and sCr)
- Volume status and blood pressure

Even though most clinicians argue for the need to monitor renal function in all patients following the initiation of SGLT2 inhibitors, a recent report published in the Clinical Journal of American Society of Nephrology (CJASN) indicates that there is no need to have a routine monitoring strategy to check kidney function or electrolytes, unless there is a clinical concern about volume depletion in specific individuals, such as in patients with BP <120/70 mm Hg, sign/symptoms of volume depletion (eg, orthostatic symptoms), a regimen of high-dose diuretics, and perhaps among elderly patients. This recommendation is predicated on the concept that the risk of AKI is not increased, eGFR dipping is not associated with kidney injury, and that ultimately dipping should not affect management or continuation of therapy. Furthermore, unlike RAAS inhibitors, SGLT2 inhibitors do not cause hyperkalemia after initiation. Therefore, patients can safely undergo blood work at a subsequent follow-up appointment to avoid additional cost and unnecessary anxiety around an eGFR dip. The authors hope that this strategy will decrease the barriers to initiating guidelines-recommended therapy, particularly in the primary care setting.[75] Monitoring renal function 4 weeks after initiating SGLT2 inhibitors is recommended for high-risk patients (prior episodes of kidney injury, advanced CKD and patients at risk of volume depletion). If serum creatinine rose >30% of baseline value, clinicians need to reassess blood pressure and volume status with consideration to reduce/hold diuretics, liberalize fluid intake or holding SGLT-2 inhibitors.

Clinicians should ask patients who are taking insulin or insulin secretagogues to monitor fasting and pre-meal glucose levels for the first few weeks following initiation or dose escalation of dapagliflozin.

Insulin dosing should be decreased by 10% to 20% and insulin secretagogue dosing by 50% if blood glucose fall <80 mg/dL.

Use of Dapagliflozin in Special Situations

Use in the Elderly

Special consideration should be given when prescribing dapagliflozin to elderly patients as they are predisposed to intravascular volume depletion. Clinicians should monitor for symptoms such as hypotension, orthostatic hypotension, dizziness, syncope, and dehydration before prescribing dapagliflozin.

The cardiovascular and renal benefits of dapagliflozin in elderly patients were evaluated in a sub-analysis of DECLARE-TIMI 58 trial, which included a large cohort of elderly and very elderly patients (65–75 and >75 years old). Similar results were noted across all age groups indicating that the overall efficacy and safety of dapagliflozin were consistent regardless of age.[76]

Dapagliflozin and Pregnancy

(SGLT2) inhibitors are not recommended for patients with type 2 diabetes mellitus planning to become pregnant. This is based on adverse effects on renal development observed in animal studies. Similarly due to the potential for serious adverse reactions in the breastfeeding infant, breastfeeding is not recommended by the manufacturer.[74] Patients of child-bearing age should use effective contraception during therapy. Transition to a preferred therapy should be initiated prior to conception and contraception should be continued until glycemic control is achieved.

Dapagliflozin in Patients Who Received Kidney Transplant

Little is known about the safety and efficacy of SGLT2i in the kidney transplant setting. Concerns regarding increased

risk of urinary tract infections, diabetic ketoacidosis and acute kidney injury limit their use in this patient population. In a single center, retrospective analysis of 50 adult kidney transplant recipients who were followed for a period of 6 months, improvement in weight (−2.95 kg [SD 3.54, P = <0.0001 (CI: 3.53, 1.50)]), hypomagnesemia (0.13 [SD 1.73, P = 0.0004 (CI: 0.06, 0.20)]) and insulin usage (−3.7 units [SD 22.8, P = 0.17]) was observed. Similar rate of UTIs was observed in patients receiving treatment compared to a control group. No incidence of DKA or amputations was observed. While conclusions cannot be accurately drawn from a single-center retrospective studies like this one and while randomized research is needed to further validate these results, this data serves as a hypothesis for future studies. In the meantime, the use of dapagliflozin should be avoided in the first-year post kidney transplant.[77]

Dapagliflozin: Current State and Future Directions

Real-world effectiveness studies have confirmed that the benefits of SGLT-2 inhibitors observed in clinical trials. CVD-REAL 3, a multinational observational cohort study, assessed kidney outcomes in 35,561 patients initiating SGLT2 inhibitors propensity matched to other glucose-lowering agents and found that SGLT2 inhibitors reduced eGFR decline by 1.53 mL/min per 1.73 m^2 per year (95% CI 1.34–1.72).[78] The efficacy and safety of dapagliflozin in patients with CKD was studied across 4 broad global regions: Asia, Europe, Latin America, and North America with no apparent effect modification by geographic region. Similar to randomized controlled trials, the composite outcome of 50% decline in eGFR, progression to ESKD or death from kidney or cardiovascular cause was lower with dapagliflozin.[79] The effect of dapagliflozin on new-onset type 2 diabetes mellitus was assessed in a pooled analysis or patient-level data from the DAPA-CKD and the DAPA-HF trials with evidence of reduction of new-onset diabetes mellitus in participants with chronic kidney disease and heart failure.[80]

According to clinicaltrials.gov, there are 183 studies in progress using dapagliflozin in different disease states. A total of 23 of these studies are specific to kidney disease. Notable among them are a study exploring dapagliflozin outcomes in advanced kidney disease stages 4 and 5, vascular impact, as well as a study looking at pharmacokinetics and dialyzability of dapagliflozin in dialysis patients. Finally, a separate study is evaluating dapagliflozin in the transplant population, IgA nephropathy patients and those with FSCG.[50]

Acknowledgment

Disclosure

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