EMPA-REG OUTCOME: The Nephrologist’s Point of View

Christoph Wanner, MD
Department of Medicine, Division of Nephrology, Würzburg University Clinic, Germany.

ABSTRACT

There is increasing evidence that sodium glucose cotransporter 2 (SGLT2) inhibitors have renoprotective effects, as demonstrated by the renal analyses from clinical trials including Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), CANagliflozin Treatment And Trial Analysis versus SUlphonylurea (CANTATA-SU), and the dapagliflozin renal study. The potential mechanisms responsible are likely multifactorial, and direct reno-vascular and hemodynamic effects are postulated to play a central role. This report reviews the renal outcomes data from key SGLT2 inhibitor clinical trials, discusses the hypotheses for SGLT2 inhibitor-associated renoprotection, and considers the main renal safety issues associated with SGLT2 inhibitor treatment.

KEYWORDS: Canagliflozin; Dapagliflozin; Empagliflozin; Renal outcomes; Renoprotection; Sodium glucose cotransporter 2 inhibitors

Since the publication 15 years ago of the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, which investigated

PATHOPHYSIOLOGY OF DIABETIC KIDNEY DISEASE

In diabetes, chronic hyperglycemia causes substantial morbidity and mortality due to the resulting macrovascular disease (ie, atherosclerotic cardiovascular disease) and
microvascular disease (ie, kidney disease, retinopathy, and neuropathy). Diabetic kidney disease develops gradually over many years and has several separate but interrelated stages, including reversible glomerular hyperfiltration, normal glomerular filtration and normoalbuminuria, normal or decreasing glomerular filtration and microalbuminuria, declining glomerular filtration and macroalbuminuria, and end-stage renal disease. Several well-defined pathophysiologic mechanisms of diabetic kidney disease have been described, including hemodynamic, metabolic, and inflammatory pathways, as reviewed in detail by Toth-Manikowski and Atta. In the hemodynamic pathways of diabetic kidney disease, RAAS activation leads to increased levels of angiotensin II, causing efferent arteriolar vasoconstriction and hyperfiltration; there is also increased expression of another efferent arteriolar vasoconstrictor, endothelin-1. In terms of metabolic pathways, hyperglycemia leads to generation of free oxygen radicals, causing inhibition of glyceraldehyde-3-phosphate dehydrogenase, which prevents normal glycolysis and results in a backlog of glycolysis precursors, leading to upregulation of the polyol and hexosamine pathways and the production of advanced glycation end-product precursors and cofactors for protein kinase C activation. These metabolic effects are associated with various pathophysiologic processes affecting the kidney, including increased transcription of inflammatory cytokines, renal cell hypertrophy, increased mesangial matrix components, and damage to the glomerular basement membrane, which contribute to glomerular hyperfiltration. With regard to the inflammatory pathways, hyperglycemia results in 1) increased expression of nuclear factor-kB, a transcription factor that regulates gene expression relating to processes including inflammation, immunity, and apoptosis; 2) activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway, which relays extracellular chemical signals to gene promoters; and 3) increased expression of inflammatory cytokines, such as interleukins and tumor necrosis factor-α. Other pathways that may also contribute to diabetic kidney disease include decreased podocyte autophagic activity and upregulation of sodium glucose cotransporter 2 (SGLT2) expression, both of which are associated with hyperglycemia.

MECHANISM OF ACTION OF SGLT2 INHIBITORS
SGLT2 inhibitors are glucose-lowering agents that target the kidney to reduce the reabsorption of glucose and promote glucose excretion in the urine, thereby reducing hyperglycemia in patients with T2DM. Three SGLT2 inhibitors — canagliflozin, dapagliflozin, and empagliflozin — have been approved for the treatment of T2DM by regulatory agencies in the United States (US), European Union (EU), and other parts of the world. Three more SGLT2 inhibitors — ipragliflozin, luseogliflozin, and tofogliflozin — have regulatory approval in Japan, but are not currently available in either the US or EU markets; other SGLT2 inhibitors are in clinical development as well. The mechanism of action of SGLT2 inhibitors has been described in detail in previous reviews. Briefly, effectively all of the glucose filtered by the kidney in a healthy individual is reabsorbed and returned to the blood circulation, and a negligible amount is excreted in the urine. Renal glucose reabsorption is predominantly mediated by SGLT2, with lesser involvement by its family member SGLT1. Evidence suggests that in patients with T2DM, the expression and activity of SGLT2 is increased in the presence of hyperglycemia, resulting in additional glucose reabsorption and preservation of elevated blood glucose levels. Pharmacologic inhibition of SGLT2 in the kidney reduces the capacity for renal glucose reabsorption by up to 50%. As SGLT2 reabsorbs sodium and glucose in a cotransport manner, SGLT2 inhibitors also cause natriuresis and are associated with an antihypertensive effect. The mechanism of SGLT2 inhibition occurs independently of insulin secretion, and is not affected by pancreatic β-cell function or the degree of insulin resistance. A review of the efficacy and safety of SGLT2 inhibitors is presented by Thrasher in this issue. In addition to their glucose-lowering effect, increasing evidence suggests that SGLT2 inhibitors have renoprotective effects, as discussed below.

SUMMARY OF RENAL FUNCTION RESULTS FROM EMPA-REG OUTCOME AND OTHER PHASE III EMPAGLIFLOZIN STUDIES
The cardiovascular and renal outcomes data from EMPA-REG OUTCOME have been described. Briefly, the study population included patients with T2DM, established cardiovascular disease, and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m². Patients were randomized (N = 7020) to receive either empagliflozin (10 mg or 25 mg) or placebo once daily, in addition to standard care. Prespecified renal outcomes included incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria (defined as urinary albumin:creatinine ratio [UACR] ≥30 mg/g). Several additional prespecified renal microvascular outcomes and a post hoc renal composite outcome were also analyzed. Patients in EMPA-REG OUTCOME had the following baseline characteristics: mean age, ~63 years; mean BP, ~135/77 mm Hg; mean duration of T2DM >10 years, ~57%; baseline eGFR ≥60 and <90 mL/min/1.73 m², ~52%; received RAAS inhibition with angiotensin-convverting enzyme inhibitors or angiotensin II receptor blockers, ~80%; and UACR <30 mg/g, ~59%. The median observation period was 3.1 years. Empagliflozin treatment (10- mg and 25-mg pooled dose group) was associated with a statistically significant 39% reduction in relative risk of incident or worsening nephropathy vs placebo (Figure 1A). Statistically significant relative risk reductions for empagliflozin vs placebo were also observed for progression to macroalbuminuria, doubling of serum
creatinine levels, and the initiation of renal-replacement therapy (Figure 1B).\textsuperscript{22} No statistically significant difference in the rate of incident albuminuria between the treatment groups was observed. Events consistent with acute renal failure (including acute kidney injury) and hyperkalemia occurred less frequently in the empagliflozin group than in the placebo group.\textsuperscript{22} Mean eGFR decreased over the first 4 weeks and then stabilized in the empagliflozin group,\textsuperscript{22} which is suggestive of decreased intraglomerular pressure. At the post-treatment follow-up, after cessation of study drug, patients in the empagliflozin group (10-mg and 25-mg doses) had an adjusted mean difference from placebo in the change from baseline eGFR of 4.7 mL/min/1.73 m\textsuperscript{2} ($P < .001$ for both comparisons).\textsuperscript{22} Assuming a rate of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{(A) Kaplan-Meier analysis of incident or worsening nephropathy in EMPA-REG OUTCOME.\textsuperscript{22} Estimates of the probability of a first occurrence of a prespecified renal composite outcome of incident or worsening nephropathy among patients who received at least one dose of either empagliflozin or placebo are shown. Because of the declining numbers of patients at risk, Kaplan-Meier curves have been truncated at 48 months. (B) Risk comparison for renal outcomes in EMPA-REG OUTCOME.\textsuperscript{22} All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease. eGFR = estimated glomerular filtration rate. Reprinted from\textsuperscript{22}: Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. \textit{N Engl J Med}. 2016;375:323-334. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.}
\end{figure}
decline in eGFR of approximately 4 mL/min/1.73 m^2 per year in T2DM patients, an eGFR gain of 4.7 mL/min/1.73 m^2 could be translated into delaying the need for dialysis by approximately 1.0 year. The study concluded that empagliflozin is associated with a slower progression of diabetic kidney disease and lower rates of clinically relevant renal events vs placebo when added to standard care in patients with T2DM at high cardiovascular risk. This renal analysis was not without limitations, as it was not a dedicated renal trial, and renal events were either reported by the investigators or derived from laboratory data and not prospectively adjudicated.

Evidence of renoprotection was also observed in earlier Phase III studies of empagliflozin. When empagliflozin was added to existing glucose-lowering therapy in patients with T2DM and CKD (N = 741), U_ACR improved with empagliflozin, compared with placebo at week 52. Fewer patients receiving empagliflozin vs those receiving placebo progressed from no albuminuria to microalbuminuria, and from microalbuminuria to macroalbuminuria (eg, stage 3 CKD, eGFR ≥30 and <60 mL/min/1.73 m^2: 12.2% vs 22.2% and 2.0% vs 11.4% for empagliflozin 25 mg and placebo, respectively). More patients with stage 3 CKD receiving empagliflozin 25 mg improved from macroalbuminuria to baseline at microalbuminuria, or microalbuminuria to no albuminuria, at end of treatment (32.6% vs 8.6% and 27.5% vs 21.4% for empagliflozin 25 mg and placebo, respectively). Small decreases in eGFR were observed in the empagliflozin groups, and these returned to baseline levels by the end of the 3-week follow-up period. In a randomized controlled trial of empagliflozin (25 mg once daily, n = 769) vs glimepiride (1-4 mg once daily, n = 780) as add-on to metformin in T2DM, assessment of mean eGFR indicated that renal function was preserved from baseline to week 104 with empagliflozin. The adjusted mean difference in eGFR from baseline to week 104 for empagliflozin vs glimepiride was 3.3 mL/min/1.73 m^2 (95% confidence interval [CI], 2.0-4.7; P < .0001). Furthermore, U_ACR improved with empagliflozin compared with glimepiride.

**SUMMARY OF RENAL FUNCTION RESULTS FROM OTHER SGLT2 INHIBITOR STUDIES**

A secondary analysis of renal data from a 2-year randomized controlled trial comparing canagliflozin and glimepiride in patients with T2DM, CANagliflozin Treatment And Trial Analysis versus Sulphonylurea (CANTATA-SU; NCT00968812), was recently published. Patients were randomized (N = 1450) to receive either canagliflozin (100 mg or 300 mg) or glimepiride (up-titrated to 6-8 mg) once daily on a background of metformin therapy. Patients with eGFR ≥55 mL/min/1.73 m^2 (or ≥60 mL/min/1.73 m^2 if based on restriction of metformin use in the local label) were included in the study. Other patient characteristics at baseline were as follows: mean age, ~56 years; mean BP, ~130/79 mm Hg; mean duration of T2DM, ~6.6 years; received background RAAS inhibition, ~61%; and U_ACR <30 mg/g, ~84%. The main efficacy endpoint for this analysis was the yearly rate of decline in eGFR over 104 weeks of follow-up, and exploratory efficacy endpoints were the least squares mean change from baseline in eGFR and U_ACR. Results demonstrated that the annual rate of decline in eGFR was statistically significantly lower in both canagliflozin groups vs glimepiride (canagliflozin 100 mg: 0.5 mL/min/1.73 m^2 per year; 95% CI, 0.0-1.0; canagliflozin 300 mg: 0.9 mL/min/1.73 m^2 per year; 95% CI, 0.4-1.4; glimepiride: 3.3 mL/min/1.73 m^2 per year; 95% CI, 2.8-3.8; P < .01 for each canagliflozin group vs glimepiride). The same trend occurred in a subgroup analysis of patients with U_ACR ≥30 mg/g (n = 230; 15.9% of total population). An acute reduction in eGFR was observed for canagliflozin groups after 4 weeks of treatment, which was followed by stabilization in the rate of long-term decline in eGFR, and is similar to observations reported with empagliflozin. This is suggestive of altered renal hemodynamics and reduced intraglomerular pressure. U_ACR increased over time with glimepiride, remained stable with canagliflozin 100 mg, and decreased with canagliflozin 300 mg over year 1 to return to baseline levels at year 2. In the subgroup of patients with U_ACR ≥30 mg/g, canagliflozin (100 mg and 300 mg) significantly decreased U_ACR over time (31.7% and 49.3% reductions, respectively) relative to glimepiride. A modest and comparable improvement in blood glucose concentrations was observed across all treatment groups (glycated hemoglobin [HbA1c] reduction 0.8%-0.9% at year 1, and 0.6%-0.7% at year 2), suggesting these beneficial effects on kidney function are not mediated by blood glucose over this relatively short period. Similar proportions of patients across each treatment group (~3% for each) experienced adverse events potentially related to kidney function (not further defined). In terms of study limitations, CANTATA-SU was not a dedicated renal study and the renal events were not adjudicated. The follow-up period was 2 years, which was shorter than that for EMPA-REG OUTCOME. In addition, eGFR was not measured after drug discontinuation, so it was not possible to verify whether the initial decrease in eGFR observed in the canagliflozin group was reversible. It was further noted that the lack of a placebo arm meant that no conclusion could be made about whether canagliflozin was renoprotective or glimepiride worsened the progression of kidney disease.

A post hoc analysis of data from a 104-week randomized controlled trial of dapagliflozin (NCT00663260) included 166 patients with T2DM and stage 3 CKD with increased albuminuria (U_ACR ≥30 mg/g). Patients were randomized to receive once-daily doses of dapagliflozin 10 mg, dapagliflozin 5 mg, or placebo. More patients in the dapagliflozin groups moved to a lower U_ACR category compared with the placebo group (33.9% and 39.6% for dapagliflozin 10 mg and 5 mg, respectively, vs 15.8% for placebo); similarly, fewer patients receiving dapagliflozin compared with placebo progressed to a higher U_ACR category. In addition, more patients in the dapagliflozin groups achieved normoalbuminuria status than in the placebo group (17.8%...
and 18.9% vs 7.0% for dapagliflozin 10 mg, dapagliflozin 5 mg, and placebo, respectively.29 There was an initial decrease in eGFR within the first 4 weeks of dapagliflozin therapy and no further decline through the 104-week period.29 Renal adverse events, mostly associated with increased creatinine, occurred in 10.7% of subjects in the dapagliflozin 10-mg group, 1.9% of subjects in the dapagliflozin 5-mg group, and 3.5% of subjects in the placebo group.29 There were no between-group differences in the frequency of serious renal adverse events (~1.8%-1.9% for each).29 This analysis is limited by being post hoc and by its small sample size.29

Figure 2. A summary of possible mechanisms of renal protection associated with SGLT2 inhibitors.19 The pleiotropic effects of SGLT2 inhibition may provide cardioprotective and renal protective effects via several mechanisms: (1) SGLT2 inhibition attenuates primary proximal tubular hyper-reabsorption in the kidney in diabetes, increasing/restoring the tubuloglomerular feedback signal at the macula densa ([Na⁺/Cl⁻/K⁺] MD) and hydrostatic pressure in Bowman’s space (P Bow). This reduces glomerular hyperfiltration, beneficially affecting albumin filtration and tubular transport work, and thus, renal oxygen consumption; (2) by lowering blood glucose levels, SGLT2 inhibitors can reduce kidney growth, albuminuria, and inflammation; (3) SGLT2 inhibitors have a modest osmotic diuretic, natriuretic, and uricosuric effect, which can reduce ECV, blood pressure, serum uric acid levels, and body weight. These changes may have beneficial effects on both the renal and cardiovascular systems; (4) SGLT2 may be functionally linked to NHE3, such that SGLT2 inhibition may also inhibit NHE3 in the proximal tubule, with implications on the natriuretic, GFR, and blood pressure effect; (5) SGLT2 inhibition reduces insulin levels and the need for therapeutic or endogenous insulin and increases glucagon levels. As a consequence, lipolysis and hepatic gluconeogenesis are elevated. These metabolic adaptations reduce fat tissue/body weight and hypoglycemia risk, and result in mild ketosis, potentially having beneficial effects on both the renal and cardiovascular systems; (6) SGLT2 inhibition may also enhance renal HIF content, which may have renal protective effects. White text boxes indicate affected variables; gray text boxes indicate processes that link SGLT2 inhibition to the reduction in GFR. Green arrows demonstrate consequences; red arrows indicate changes in associated variables (increase/decrease). ECV = extracellular volume; GFR = glomerular filtration rate; HIF = hypoxia-inducible factor; NHE3 = sodium-hydrogen antiporter 3; SGLT2 = sodium glucose cotransporter 2. Reprinted from19; Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia. 2017;60:215-225. Reprinted with permission of Springer.
A recent commentary comparing the renal analyses from EMPA-REG OUTCOME and CANTATA-SU suggested that these data provide replication of renal effects and that renoprotection may be a class effect of SGLT2 inhibitors that is additive to RAAS blockade.30

POSSIBLE MECHANISMS FOR IMPROVEMENT IN RENAL FUNCTION WITH SGLT2 INHIBITORS

The potential mechanisms responsible for the improved renal outcomes observed with SGLT2 inhibition are likely to be multifactorial (Figure 2)19; direct renovascular and hemodynamic effects are postulated to have a key role.22 SGLT2 inhibition reduces proximal tubular sodium reabsorption, and thus, increases sodium delivery to the macula densa, which activates tubuloglomerular feedback and afferent arteriolar vasomodulation (Figure 3; see also renal protection video in supplemental materials),31 resulting in decreased renal blood flow and decreased glomerular hyperfiltration.31,32 SGLT2 inhibition also was found to significantly improve intraglomerular hypertension in patients with type 1 diabetes mellitus (T1DM) and renal hyperfiltration, achieving a mean intraglomerular pressure similar to that observed in T1DM patients with normal renal filtration.33 Reduced secretion of atrial natriuretic peptide may have a role in lowering intraglomerular pressure, but any relationship with SGLT2 inhibition is currently speculative.27 In addition, treatment with an SGLT2 inhibitor in a mouse model of T1DM prevented diabetes-induced increases in GFR, attenuated albuminuria, and reduced markers of kidney hypertrophy and inflammation.32 Renal hemodynamic changes that reduce glomerular hyperfiltration and intraglomerular pressure are manifested clinically as acute reductions in albuminuria and eGFR, followed by longer-term eGFR stabilization, and should equate to improved long-term kidney outcomes.27 Meta-analyses of clinical trial data suggest that a 30% reduction in albuminuria was associated with a 24% reduction in the risk of end-stage renal disease,34 assuming other markers of kidney disease were stable.27 Reductions in vascular stiffness35,36 and vascular resistance35 associated with SGLT2 inhibitor therapy may also contribute to the observed improvements in renal disease progression.22

The effect of systemic or renal neurohormonal factors on renal outcomes associated with SGLT2 inhibitor therapy should also be considered.36,37 Data from SGLT2 inhibitor...

![Figure 3](http://circ.ahajournals.org/content/129/5/587)

Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT2 inhibition reduces hyperfiltration via TGF

---

**Figure 3** Possible renal hemodynamic effects associated with SGLT2 inhibition.31 Under physiological conditions, TGF signaling maintains stable GFR by modulation of preglomerular arteriole tone. In cases of conditional increases in GFR, the macula densa within the juxtaglomerular apparatus senses an increase in distal tubular sodium delivery and adjusts GFR via TGF accordingly (A); under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT2-mediated reabsorption of sodium (Na+) and glucose impairs this feedback mechanism. Thus, despite increased GFR, the macula densa is exposed to lowered sodium concentrations. This impairment of TGF signaling likely leads to inadequate arteriole tone and increased renal perfusion (B); and SGLT2 inhibition with empagliflozin treatment blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium delivery to the macula densa. This condition restores TGF via appropriate modulation of arteriolar tone (eg, afferent vasoconstriction), which, in turn, reduces renal plasma flow and hyperfiltration (C). GFR = glomerular filtration rate; SGLT2 = sodium glucose cotransporter 2; TGF = tubuloglomerular feedback. Reprinted from31; Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587-597. Available at: http://circ.ahajournals.org/content/129/5/587. Reprinted with permission.
### Use of Canagliflozin, Dapagliflozin, and Empagliflozin in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US Label — Prescribing Information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assess renal function prior to initiating SGLT2 inhibitor treatment and periodically thereafter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose adjustment and more frequent renal function monitoring are recommended in patients with eGFR &lt; 60 mL/min/1.73 m²</strong></td>
<td>No dose adjustment is needed in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m²)</td>
<td>No dose adjustment is needed if eGFR ≥ 45 mL/min/1.73 m²</td>
</tr>
<tr>
<td><strong>Limit dose of canagliflozin to 100 mg once daily in patients with moderate renal impairment with an eGFR 45 to &lt; 60 mL/min/1.73 m²</strong></td>
<td>Dapagliflozin should not be initiated in patients with an eGFR &lt; 60 mL/min/1.73 m²</td>
<td>Empagliflozin should not be initiated in patients with an eGFR &lt; 45 mL/min/1.73 m²</td>
</tr>
<tr>
<td><strong>Canagliflozin should not be initiated in patients with an eGFR &lt; 45 mL/min/1.73 m²</strong></td>
<td>Dapagliflozin is not recommended in patients with an eGFR persistently between 30 and &lt; 60 mL/min/1.73 m²</td>
<td>Discontinue empagliflozin if eGFR is persistently &lt; 45 mL/min/1.73 m²</td>
</tr>
<tr>
<td><strong>Canagliflozin is not recommended when eGFR is persistently &lt; 45 mL/min/1.73 m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors are contraindicated in patients with severe renal impairment (eGFR &lt; 30 mL/min/1.73 m²), ESRD, or on dialysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EU Label — Summary of Product Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assess renal function prior to initiating SGLT2 inhibitor treatment and at least annually thereafter; prior to initiating concomitant medication that may reduce renal function and periodically thereafter; at least 2-4 times/year for renal function approaching moderate renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy of SGLT2 inhibitor treatment is dependent on renal function: efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No dose adjustment is needed in patients with an eGFR 60 to &lt; 90 mL/min/1.73 m² or CrCl 60 mL/min to &lt; 90 mL/min</strong></td>
<td>No dose adjustment is indicated in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m² or CrCl ≥ 60 mL/min)</td>
<td>No dose adjustment is needed in patients with an eGFR ≥ 60 mL/min/1.73 m² or CrCl ≥ 60 mL/min</td>
</tr>
<tr>
<td><strong>Canagliflozin should not be initiated in patients with an eGFR &lt; 60 mL/min/1.73 m² or CrCl &lt; 60 mL/min</strong></td>
<td>Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (eGFR &lt; 60 mL/min/1.73 m² or CrCl &lt; 60 mL/min)</td>
<td>Empagliflozin should not be initiated in patients with an eGFR &lt; 60 mL/min/1.73 m² or CrCl &lt; 60 mL/min</td>
</tr>
<tr>
<td><strong>In patients tolerating canagliflozin with an eGFR persistently &lt; 60 mL/min/1.73 m² or CrCl &lt; 60 mL/min, dose should be adjusted to or maintained at 100 mg once daily</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canagliflozin should not be used in patients with an eGFR &lt; 45 mL/min/1.73 m² or CrCl &lt; 45 mL/min</strong></td>
<td>Dapagliflozin should be discontinued if eGFR &lt; 60 mL/min/1.73 m² or CrCl &lt; 60 mL/min</td>
<td>Empagliflozin should be discontinued when eGFR is persistently &lt; 45 mL/min/1.73 m² or CrCl is persistently &lt; 45 mL/min</td>
</tr>
<tr>
<td><strong>Canagliflozin should be discontinued when eGFR is persistently &lt; 45 mL/min/1.73 m² or CrCl is persistently &lt; 45 mL/min</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT2 inhibitors should not be used in patients with ESRD or on dialysis, as these agents are not expected to be effective in these patients.

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; SGLT2 = sodium glucose cotransporter 2.
studies in T1DM and T2DM demonstrated an increase in circulating RAAS mediators (angiotensin II, aldosterone). Empagliflozin had no significant effects on vagal tone and sympathetic nervous system activity during clamped euglycemia and hyperglycemia in patients with T1DM.

Small reductions in serum uric acid levels were observed with empagliflozin treatment during EMPA-REG OUTCOME and may be involved in the cardiovascular and renal benefits reported. The exact role is currently unclear; however, there is evidence from observational studies that elevated uric acid levels can cause hypertension, vascular damage, and impaired renal function. Adequately powered randomized clinical trials are required to fully evaluate the effects of uric acid reduction on renal outcomes.

Modest reductions in BP and body weight are associated with SGLT2 inhibitor therapy and are believed to be attributable, at least in part, to SGLT2 inhibitor-associated natriuresis. It is also possible that decreased sodium reabsorption could affect proximal tubular cell energetics and, by extension, influence other functions of these metabolically active cells.

Glucagon may have an important role in maintaining heart and kidney function. At relatively high doses, glucagon induces vasodilation with concomitant increases in renal plasma flow, eGFR, and electrolyte excretion; these changes are more evident in patients with diabetes, which may be due to the modified insulin-to-glucagon ratio. Glucagon is responsible for the increase in natriuresis in the fasting state, and has direct action (with vasopressin) in protein-induced hyperfiltration and the excretion of nitrogen end products. Empagliflozin has been shown to increase blood glucagon levels (and endogenous glucose production) in patients with T2DM.

The activation of hypoxia-inducible factor 1 (HIF-1) and subsequent erythropoiesis may also confer renal protective effects. HIF-1, consisting of an oxygen-sensitive α subunit and a constitutively expressed β subunit, is a key protein that regulates protective cellular responses in the kidney (and other organs) to hypoxia; erythropoiesis is one of several biological processes related to kidney function that is regulated by HIF-1. A recent in vitro study reported that dapagliflozin induces HIF-1 in murine ischemic renal tissue and human ischemic cultured renal tubular cells. It is plausible that a HIF-1-induced increase in erythropoietin — related to SGLT2 inhibition — could lead to a subsequent improvement in oxygen delivery and other associated renal protective effects.

Lastly, SGLT2 inhibitor-associated changes in blood volume or renal perfusion may alter serum creatinine turnover and renal function assessments; however, further research is required.

RENALE SAFETY WITH SGLT2 INHIBITORS AND USE IN PATIENTS WITH RENAL IMPAIRMENT

General safety issues associated with SGLT2 inhibitors are discussed in the review by Thrasher in this issue. Following postmarketing reports of acute kidney injury with SGLT2 inhibitor treatment, the US Food and Drug Administration reinforced the existing warning in the respective drug labels to include information on this potential risk and recommendations for its minimization.

There was no association between empagliflozin and increased risk of acute kidney injury in the EMPA-REG OUTCOME study. Overall safety signals seen in observational studies (real-world observations) are potentially confounded by concomitant treatment or other conditions that may bias the findings. Nonetheless, clinicians should consider factors that may predispose patients to acute kidney injury prior to therapy initiation (eg, hypovolemia, chronic renal insufficiency, concomitant medications, such as diuretics), consider temporary discontinuation of SGLT2 inhibitor treatment during periods of reduced oral intake or fluid loss, and discontinue therapy promptly and institute treatment if acute kidney injury should occur.

SGLT2 inhibition has been evaluated in clinical trials of patients with T2DM and various stages of CKD. In a review of clinical trial data by Scheen, clinical efficacy of SGLT2 inhibitors in terms of HbA1c reduction was maintained in patients with mild CKD (stage 2; eGFR 60-89 mL/min/1.73 m²), decreased in patients with moderate CKD (stage 3a and 3b; eGFR 45-59 mL/min/1.73 m², and 30-44 mL/min/1.73 m², respectively), particularly stage 3b, and was virtually eliminated in those with severe CKD (stage 4; eGFR 15-30 mL/min/1.73 m²). The short-term reductions in eGFR that were observed in clinical trials with canagliflozin, dapagliflozin, and empagliflozin are suggestive of an early hemodynamic effect of treatment that becomes attenuated over time, and do not imply the development of progressive renal injury.

Subgroup analysis of cardiovascular outcomes from EMPA-REG OUTCOME showed consistent benefit in patients with low eGFR vs those with higher or normal eGFR levels. It should be noted that SGLT2 inhibitor agents are contraindicated in patients with severe renal impairment; details from US and EU labels on the use of canagliflozin, dapagliflozin, and empagliflozin in patients with varying degrees of renal impairment are summarized in the Table. This labeling reflects that urinary glucose excretion, and thus, the glucose-lowering efficacy of SGLT2 inhibitors, decreases with increasing renal impairment (ie, as eGFR declines). In addition, the risk of renal-related adverse events increases with declining eGFR.

CONCLUSION

The renal benefits of SGLT2 inhibitors, as well as the cardiovascular benefits of empagliflozin, should be considered by physicians when selecting glucose-lowering medication for the management of patients with T2DM and high cardiovascular risk. The renal findings from clinical trials of empagliflozin, canagliflozin, and dapagliflozin can be assessed definitively when data from 2 ongoing renal outcomes trials are published; namely, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; NCT02065791), and...
Another renal study to investigate the effect of dapagliflozin on albuminuria in stage 3 CKD is recruiting participants (NCT02547935).\(^{51}\) Given the renal results from EMPA-REG OUTCOME, questions about treatment risk and benefit may extend to patients with diabetic kidney disease who are not at high cardiovascular risk. Specifically, physicians may wish to consider the use of empagliflozin for the treatment of diabetic kidney disease and albuminuria in a patient without a prior cardiovascular event but with declining renal function, and not postpone such treatment until the patient has survived a myocardial infarction. However, this approach will require additional studies before a firm recommendation can be determined for this patient population. In conclusion, the results from EMPA-REG OUTCOME, CANTATA-SU, and the dapagliflozin renal study about renal protective outcomes are encouraging, and indicate that SGLT2 inhibitor agents offer a promising therapeutic option in the future management of patients with T2DM.

References


