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# Efficacy and Renal Outcomes of SGLT2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease

Michael S. Kelly

*Chapman University*, [mkelly@chapman.edu](mailto:mkelly@chapman.edu)

Jelena Lewis

*Chapman University*, [jelewis@chapman.edu](mailto:jelewis@chapman.edu)

Ashley M. Huntsberry

*University of Colorado*

Lauren Dea

*Kindred Hospital*

Ivan Portillo

*Chapman University*, [iportillo@chapman.edu](mailto:iportillo@chapman.edu)

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# Efficacy and Renal Outcomes of SGLT2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease

## **Comments**

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**Title:** Efficacy and renal effects associated with GLP-1 receptor agonists and SGLT2 inhibitors among patients with type 2 diabetes and chronic kidney disease.

**Authors:**

Michael S. Kelly, Pharm.D.

Assistant Professor, Department of Pharmacy Practice

Chapman University School of Pharmacy

Irvine, CA

Jelena Lewis, Pharm.D.

Assistant Professor, Department of Pharmacy Practice

Chapman University School of Pharmacy

Irvine, CA

Ashley M. Huntsberry, Pharm.D.

Assistant Professor, Department of Clinical Pharmacy\_\_

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Aurora, CO

Lauren Dea, Pharm.D.

Pharmacy Practice Resident

Kindred Hospital

La Mirada, CA

Ivan Portillo, MLIS, AHIP

Chapman University

Orange, CA

**Corresponding Author:**

Michael S. Kelly  
9401 Jeronimo Rd.  
Irvine, CA 92604  
Telephone: 714-516-5423  
Email: [mkelly@chapman.edu](mailto:mkelly@chapman.edu)

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**Abstract:**

**Objective:** To review glucose-lowering efficacy and changes in renal function associated with GLP-1 receptor agonists and SGLT2-Inhibitors among patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM).

**Data Sources:** A literature search of MEDLINE and Cochrane databases was performed from 2000 to March 2018 using search terms: *SGLT2 inhibitors, sodium glucose co-transporter 2, canagliflozin, empagliflozin, dapagliflozin, glucagon-like peptide-1 receptor agonists, GLP-1, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, semaglutide, and chronic kidney disease*. References of identified articles were also reviewed.

**Study Selection and Data Extraction:** English-language studies investigating glucose-lowering endpoints and/or changes in renal function with a U.S. approved SGLT2 inhibitor or GLP-1 receptor agonist were included.

**Data Synthesis:** GLP-1 agonists and SGLT2-Inhibitors effectively lower glucose in patients with T2DM and CKD. Both agents have demonstrated short-term renoprotective effects by slowing progression of albuminuria and decreasing urine albumin-to-creatinine values.

**Relevance to Patient Care and Clinical Practice:** This review highlights the glucose-lowering efficacy and reported renal benefits of GLP-1 agonists and SGLT2-Inhibitors when used in patients with T2DM and CKD. Given that these comorbidities are associated with increased cardiovascular risk, we believe that these agents should be the preferred add-on agents in most patients with uncontrolled T2DM and CKD.

**Conclusions:** In patients with T2DM and CKD, GLP-1 agonists and SGLT2-Inhibitors are effective in lowering glucose, preventing progression of worsening albuminuria, and may reverse the

level of albuminuria. Ongoing studies will provide additional information as to whether these agents will become standard of care in treating patients with T2DM and CKD.

### **Introduction:**

Chronic kidney disease (CKD), defined as reduced estimated glomerular filtration rate (eGFR) and/or presence of increased albuminuria (urinary albumin-to-creatinine ratio >30 mg/g) for at least 3 months, is a common comorbidity of diabetes mellitus (DM).<sup>1</sup> While CKD may result from multiple etiologies, long-term uncontrolled DM is a major risk factor for diabetic kidney disease, as well as the most common cause of CKD and the leading cause of end-stage-renal disease globally.<sup>2,3</sup> The most recent estimates from the United States Renal Data System (USRDS) report that approximately 40% of patients with CKD also have concomitant DM.<sup>4</sup> Given that DM and CKD are both associated with increased morbidity and mortality, multi-interventional approaches are recommended to reduce the progression of worsening albuminuria and kidney dysfunction, as well as lower risk of cardiovascular events. Such approaches include achieving blood pressure <130/80 mm Hg,<sup>1,5</sup> use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients with CKD and albuminuria, as well as maintaining glycemic control.<sup>1,5</sup>

Patients with type 2 DM (T2DM) may achieve glycemic control with a combination of oral and injectable medications. Current standards for treating T2DM recommend choosing additional

antihyperglycemic therapies based on several patient-specific factors, including efficacy of lowering hemoglobin A1C (A1C), cost, risk of hypoglycemia, and potential for weight gain. Metformin remains the preferred first agent for most patients with T2DM due to effective A1C-lowering, low hypoglycemia risk, neutral weight gain, and low cost. Metformin is primarily renally eliminated, thus contraindicated in patients with an eGFR <30 ml/min/1.73m<sup>2</sup>.<sup>5</sup> In patients with T2DM and CKD, renal function must also be considered as many of the available second-line antihyperglycemic agents require dose reduction in the setting of reduced renal function, or are not recommended for continued use in patients with eGFR <45 ml/min/1.73m<sup>2</sup> (Table 1).

Recent cardiovascular outcomes trials (CVOT) have reported reduced risk of major cardiovascular events with select oral antihyperglycemic agents. Trials evaluating sodium-glucose co-transporter-2 inhibitors (SGLT2-I) empagliflozin and canagliflozin, and glucagon-like peptide-1 receptor agonist (GLP-1RA), liraglutide, each reported reduced risk of a primary composite endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke compared to placebo when added to standard antihyperglycemic treatment in patients with T2DM.<sup>6-8</sup> Each trial included a subset of patients with CKD and reported on prespecified renal outcomes, although not as a primary study endpoint. In the EMPA-REG trial,<sup>6</sup> 26% of patients had an eGFR <60 ml/min/1.73m<sup>2</sup> and nearly 40% had some degree of albuminuria. Compared to placebo, empagliflozin was associated with a 38% reduction in progression to macroalbuminuria and 44% reduction in doubling serum creatinine. In the CANVAS studies<sup>8</sup>, 30.2% had some degree of albuminuria, the majority defined as microalbuminuria. Improved

renal outcomes associated with canagliflozin included a 27% reduced risk of albuminuria progression, and lower risk of a composite renal outcome including consistent 40% reduction in eGFR, need for renal replacement therapy, or renal death. Regression of albuminuria also occurred more frequently in those who received canagliflozin compared to placebo. Lastly, the LEADER<sup>7</sup> trial included 21% of subjects with eGFR 30-59 ml/min/1.73m<sup>2</sup>, and even included a small sample of patients (2.4%) with eGFR<30 ml/min/1.73m<sup>2</sup>. The composite renal endpoint of new macroalbuminuria or doubling of serum creatinine with eGFR <45 ml/min/1.73m<sup>2</sup>, need for renal replacement therapy, or renal death was reduced by 22% in subjects who received liraglutide vs placebo, but occurred at relatively low rates in each group (1.5% vs 1.9%, respectively).

Given that canagliflozin, empagliflozin, and liraglutide all demonstrated lower risk of major cardiovascular events, as well as potential improvements in renal outcomes, these agents may be preferred therapies in patients with T2DM and CKD. The objective of this article is to review available evidence assessing the efficacy and potential renoprotective effects of SGLT2-I and GLP-1RAs in patients with CKD and T2DM.

## **Methods**

### **Data Sources**

A search was conducted using PubMed and Cochrane databases to identify studies from 2000 to March 7, 2018 pertaining to the safety and efficacy of SGLT2-I and GLP-1RA among patients



with CKD. Mesh terms and keywords used in the search included, “SGLT2 inhibitors”, “sodium glucose co-transporter 2”, “canagliflozin”, “empagliflozin”, “dapagliflozin”, “Glucagon-Like Peptide-1 Receptor/agonists”, “GLP-1”, “exenatide”, “liraglutide”, “albiglutide”, “dulaglutide”, “lixisenatide”, “semaglutide”, “kidney disease”, and “chronic kidney disease”. PubMed search filters were applied for English language, humans, and adults aged  $\geq 18$  years. References of identified articles were reviewed to identify any additional studies not found in the initial search. In order to limit results to only clinical trials, the search filter for clinical queries was applied.<sup>9</sup> Article selection and screening process is depicted in Figure 1.

### **Study Selection**

Studies were included if they reported outcomes related to glucose-lowering efficacy and/or renal endpoints for U.S. approved SGLT2-I or GLP-1RA in a study population of T2DM and CKD, defined as an eGFR  $< 60$  ml/min and/or urine albumin-to-creatinine ratio  $> 30$  mg/g (or equivalent). Pre-post studies were eligible if they reported baseline and follow up changes. Trials including patients with CKD and normal kidney function could be considered if full data for the CKD population was presented separate from the study population as a whole. Secondary analysis of a CKD populations from primary trials were also eligible. Published abstracts, editorials, and letters to the editor were not included in this review.

## Results

Potential articles were reviewed by three authors (MK, JL, AH) to determine eligibility. Eight studies met our inclusion criteria and are summarized in Table 2. Three studies evaluated liraglutide, while five studies evaluated SGLT2-I (canagliflozin, dapagliflozin, and empagliflozin).

Of the eight included studies, all but one was a randomized-control trial<sup>10</sup>. Five studies employed a placebo group against active treatment (SGLT2-I or GLP-1RA)<sup>11-15</sup>, one study compared SGLT2-I or to glimepiride treatment<sup>16</sup>, and one study compared GLP-1RA added to insulin therapy vs insulin therapy alone<sup>17</sup>. Efficacy of SGLT2-I or GLP-1RA was assessed by change in A1C in seven studies<sup>10-15,17</sup>, along with change in fasting plasma glucose in five studies.<sup>11-15</sup> Renal endpoints of change in eGFR were assessed in five studies<sup>10,11,13,14,16</sup>, and all eight studies assessed change in urine protein-to-creatinine (UPCR) or urine albumin-to-creatinine ratio (UACR).

### **Glucagon-like peptide-1 (GLP-1) receptor agonists**

Currently there are six GLP-1RA available in the US, including exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide, and albiglutide. GLP-1RA lower glucose by several mechanisms, including increasing insulin secretion, decreasing glucagon secretion, slowing gastric emptying, and increasing satiety. All GLP-1RA are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Liraglutide now carries an additional indication for reduced risk of major cardiovascular events in adults with T2DM and clinical cardiovascular

disease. Renal dose adjustment is not required for most GLP-1RA, except exenatide and lixisenatide (Table 1). Exenatide is not indicated in patients with eGFR <30mL/min/1.73m<sup>2</sup>, while lixisenatide should not be used in patients with eGFR <15mL/min/1.73m<sup>2</sup>.<sup>5</sup>

### **Efficacy and Renal Effects of GLP-1RA in Patients with CKD**

The Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With T2DM and Moderate Renal Impairment (LIRA-RENAL) trial evaluated liraglutide efficacy and safety over a 26-week period when added on to existing antihyperglycemic therapy in patients with uncontrolled T2DM and moderate renal impairment<sup>11</sup>. This double-blind, placebo-controlled trial included 279 patients with a mean age approximately 67 years and an A1C of ~8%. Patients were randomized to daily liraglutide or placebo subcutaneous injection. Approximately 43% of patients in each group had an eGFR 30-44 mL/min/1.73m<sup>2</sup>, 56% of patients had an eGFR of 45-59 mL/min/1.73m<sup>2</sup>, and mean UACR was 55.5 mg/g for the liraglutide group and 69.8 mg/g for the placebo group. The primary endpoint was change in baseline A1C to week 26; changes in fasting plasma glucose (FPG) from baseline to week 26 were also assessed. After 26 weeks, A1C was reduced -1.05% in the liraglutide group vs. -0.38% in the placebo group (p<0.0001). Estimated mean change in FPG from baseline to 26 weeks was -22.0 mg/dL with liraglutide vs. -10.3 mg/dL with placebo (p=0.036). Changes in renal function (eGFR and UACR) were measured from baseline to 26 weeks. The mean observed change in eGFR after 26 weeks was -0.35 mL/min/1.73m<sup>2</sup> in the liraglutide group versus 0.37 mL/min/1.73m<sup>2</sup> in the placebo group, which resulted in an estimated treatment ratio of 0.98 (p=0.36). The ratio of UACR values at week 26 compared to baseline were 0.87 with liraglutide,

compared to 1.05 with placebo, however this difference was not statistically significant ( $p=0.19$ ). The study concluded that liraglutide is effective in improving glycemic control, without affecting renal function.<sup>11</sup>

A single-arm study of 23 Japanese patients with T2DM evaluated the A1C-lowering effect and progression of diabetic nephropathy (DN) and proteinuria following 12-month treatment with liraglutide.<sup>10</sup> Patients had a mean age of 58.2 years, mean A1C of 7.4% at baseline and all patients had overt DN (defined as UPCR  $>0.5$  g/g) prior to study entry, with baseline UPCR of 2.53 g/g (or 2530 mg/g). No comparator arm was used in this study, rather a pre/post design. A significant decrease in A1C was observed at all time points. Baseline A1C was reduced from 7.4% to 7.0% after 1 month ( $p<0.001$ ), 6.6% by month 6 ( $p<0.001$ ), and 6.9% by month 12 ( $p<0.05$ ). Baseline UPCR decreased to 1.62 g/g at 1 month ( $p<0.001$ ), 1.45 g/g at 6 months ( $p<0.001$ ), and finally 1.47 g/g at 12 months ( $p<0.01$ ). The study also found a strong correlation between baseline proteinuria and changes in proteinuria after 12 months of liraglutide therapy ( $r=0.84$ ,  $p<0.0001$ ). Changes in eGFR were minimal over the 12-month study period, as eGFR decreased slightly from 58.2 mL/min/1.73m<sup>2</sup> at baseline to 56.9 mL/min/1.73m<sup>2</sup> after 12 months. Annual rates of eGFR decline were improved with liraglutide, decreasing from -6.6 mL/min/1.73m<sup>2</sup>/year prior to liraglutide initiation, to -0.33 mL/min/1.73m<sup>2</sup>/year ( $p=0.003$ ) after one year of liraglutide. Thus, with a significant decline in proteinuria and improved eGFR decline, authors concluded that for patients with T2DM and overt DN, addition of liraglutide is useful for decreasing A1C as well as slowing the progression of DN.<sup>10</sup>

A third single-center, open-label trial evaluated changes in several cardiometabolic markers, including albuminuria, with liraglutide in patients with T2DM treated with insulin.<sup>17</sup> Seventeen patients were randomized to either liraglutide titrated up to 0.9 mg/day plus insulin (8 patients) or insulin treatment only (9 patients). In addition to insulin, patients in each cohort were also receiving oral antihyperglycemic agents. Mean age was 59 years and a greater proportion of males (63%) were randomized to receive liraglutide compared to the control group (33%). Mean eGFR was >60 ml/min/1.73m<sup>2</sup> in both groups, but albuminuria was present in both study cohorts. Mean baseline A1C was 8.2% in the liraglutide group and 7.9% in the placebo group, and both groups were receiving daily insulin doses of about 0.5 units/kg/day. Mean A1C and weight were significantly reduced in the liraglutide group after 12, 24, and 36 weeks of treatment. At week 24, baseline A1C values had fallen from 8.2% to 7.5% in patients receiving liraglutide compared with an increase from 7.9% to 8.1% in the control group (p=0.0035). No data on fasting or post-meal plasma glucose were reported. Mean UACR levels at baseline were 220 mg/g in the liraglutide group and 254 mg/g in the control group, consistent with albuminuria. Compared to placebo, liraglutide was associated with significantly decreased mean UACR at week 12 (343 mg/g vs 76 mg/g; p=0.050), week 24 (310 mg/g vs 91 mg/g; p=0.016), and week 36 (226 mg/g vs 32 mg/g; p=0.022). The authors concluded that when added to baseline insulin therapy in patients with T2DM, liraglutide favorably improves glycemic control, body weight, inflammatory markers, and albuminuria.<sup>17</sup>

### **Sodium-Glucose Co-transporter Type 2 (SGLT2) inhibitors**

Currently four SGLT2-I (canagliflozin, dapagliflozin, empagliflozin, and most recently ertugliflozin) are approved to improve glucose in adults with T2DM as adjunct to diet and exercise. As a class, the SGLT2-I increase urinary glucose excretion by blocking the reabsorption of glucose in the renal proximal tubule. As SGLT2-I exert their effect in the kidneys, there are specific dose adjustments based upon renal function according to each medication's prescribing information (Table 1). Renal function should be assessed prior to initiation of SGLT2-I and periodically thereafter to ensure adequate renal function. The recommended eGFR range for continued SGLT2-I use varies among agents, but all are contraindicated when eGFR <30 mL/minute/1.73 m<sup>2</sup>.<sup>5</sup>

### **Efficacy and Renal Effects of SGLT2-I in Patients with CKD**

The Efficacy and safety of empagliflozin added to existing anti-diabetes treatment in patients with T2DM and chronic kidney disease (EMPA-REG-RENAL) trial was a multicentered, randomized, double-blind, parallel-group trial, designed to assess the efficacy and safety of empagliflozin in patients with CKD stages 2-4 and T2DM.<sup>12</sup> Full efficacy and renal outcomes data were available for CKD stages 2 (n=290) and 3 (n=374), but not stage 4 (n=74). Patients with CKD stage 3 (eGFR  $\geq$ 30 to <60 mL/min per 1.73 m<sup>2</sup>) were randomized to receive empagliflozin 25 mg or placebo for 52 weeks. Patients in this CKD subgroup had a mean age of 64.9 years, and baseline eGFR of 44.9 mL/min per 1.73 m<sup>2</sup>. The primary efficacy endpoint was change in A1C from baseline to week 24. Changes in FPG, body weight, and BP were also examined as secondary endpoints. Changes in eGFR and UACR throughout the study were evaluated as safety endpoints.

In the stage 3 CKD subgroup, the adjusted mean change in A1C from baseline to week 24 was -0.42% for empagliflozin 25 mg vs. placebo ( $p < 0.0001$ ). The A1C-lowering effect remained at week 52, with mean A1C reduction of -0.44% compared to placebo ( $p < 0.0001$ ). Adjusted treatment differences for empagliflozin vs placebo were also significantly lower for FPG at both 24 weeks (-1.1 mmol/L;  $p < 0.001$ ) and 52 weeks (-0.7 mmol/L;  $p = 0.0037$ ). In addition to reduced A1C and FPG, there was also a significant decrease in body weight and BP with empagliflozin versus placebo. Compared to placebo, a greater reduction in UACR from baseline to 52 weeks was reported with empagliflozin (-183.78 mg/g;  $p = 0.0031$ ). Although not a specified endpoint of this trial, fewer patients randomized to empagliflozin progressed from normal UACR to microalbuminuria (UACR 30-299 mg/g) compared to placebo (12.2% vs. 22.2%) and from microalbuminuria to macroalbuminuria (UACR  $\geq 300$  mg/g) (2.0% vs. 11.4%). Additionally, a greater proportion of patients with baseline macroalbuminuria improved to microalbuminuria with empagliflozin (32.6%) compared to those who received placebo (8.6%). This study was one of the first trials to report improved glycemic control and improved albuminuria status in patients with T2DM and CKD.<sup>12</sup>

A second multicenter placebo-controlled, double-blind clinical trial evaluated the efficacy and safety of dapagliflozin in patients with T2DM and moderate renal impairment (eGFR 30 to 59 mL/min per 1.73m<sup>2</sup>) and included a small percentage of patients with eGFR  $\geq 60$  mL/min per 1.73m<sup>2</sup> (4.4%) and eGFR  $< 30$  mL/min per 1.73m<sup>2</sup> (4.0%) at baseline. Patients were similar in baseline characteristics for each study group. Mean age ranged from 66-68 years, and baseline

A1C differed by study group and ranged from 8.22% to 8.53%. All patients had a mean UACR >60 mg/g, and over two-thirds of patients had diagnosed DN at baseline. Patients were randomized to receive dapagliflozin 5 mg, 10 mg, or placebo for at least 24 weeks in addition to other pre-enrollment antihyperglycemic therapies. Patients who completed the first 24 weeks of therapy were eligible to continue for an additional 28 weeks, then an additional extension period of 52 weeks (total of 104 weeks). There were 252 patients randomized, 202 entered the study for an additional 28 weeks, and 139 patients completed 104 weeks of the extension period. The primary endpoint was mean change in A1C from baseline to 24 weeks; change in FPG from baseline to week 24 was also evaluated. At the end of week 24, there was no statistically significant difference in the mean change in A1C for dapagliflozin 5 mg compared to placebo (-0.41% vs. -0.32%; p=0.561) or dapagliflozin 10 mg vs placebo (-0.44% vs. -0.32%; p=0.435). Both doses of dapagliflozin reduced FPG from baseline to 24 weeks more than placebo, however statistical significance was evaluated. In a post-hoc analysis of baseline CKD status, dapagliflozin produced a larger reduction in the adjusted A1C change and FPG in patients with CKD stage 3A compared to stage 3B from baseline to week 24 versus placebo. Numerically lower reductions in eGFR from baseline to week 24 were reported in the placebo group (-0.25 mL/min/1.73m<sup>2</sup>) compared to dapagliflozin 5 mg (-2.38 mL/min/1.73m<sup>2</sup>) and 10 mg (-4.80 mL/min/1.73m<sup>2</sup>). By week 104, changes in eGFR were similar between placebo (-2.38 mL/min/1.73m<sup>2</sup>) and dapagliflozin 5 mg (-1.71 mL/min/1.73m<sup>2</sup>) and 10 mg (-3.50 mL/min/1.73m<sup>2</sup>), however no statistical significance was reported for either time period. Patients receiving dapagliflozin were more likely to experience a shift to a lower UACR category than patients receiving placebo (22.6% vs. 10.7%). Lastly, fewer patients receiving dapagliflozin



5 or 10 mg compared to placebo experienced a UACR value >1800 mg/g during the 104-week treatment (10.8%, 9.5%, and 13.3%, respectively). The results of this trial contrast to those from the EMPA-REG-RENAL trial in that dapagliflozin did not demonstrate significant A1C-lowering efficacy among patients with T2DM and CKD. Dapagliflozin did appear to improve UACR more than placebo, but again was not a primary endpoint of this trial.

Three trials have evaluated the efficacy and safety of canagliflozin in patients with T2DM and CKD. The first study published in 2013 was a randomized, double-blind, placebo-controlled, phase 3 trial conducted across 89 centers in 19 countries.<sup>14</sup> The study included 269 patients with T2DM and stage 3 CKD (eGFR  $\geq 30$  to  $< 50$  mL/min/1.73m<sup>2</sup>). Patients had a mean age of 68.5 years and A1C of 8.0%. Baseline mean was eGFR 39.4 mL/min/1.73m<sup>2</sup> with mean UACR of 30.0 mg/g. Patients were randomized to canagliflozin 100 mg, 300 mg, or placebo daily to assess the change in A1C at week 26 compared to baseline. Both doses of canagliflozin (100 and 300 mg) produced a significant reduction in mean A1C from baseline in arms compared to placebo (-0.33% vs. -0.03%;  $p < 0.05$ ) and (-0.44% vs. -0.03%;  $p < 0.01$ ), respectively. Changes in FPG from baseline to week 26 were numerically lower for both canagliflozin 100 vs placebo, although neither reached statistical significance. Each study group experienced a decrease in eGFR, but reductions were larger in both the canagliflozin 100 and 300 mg groups compared to placebo (mean percent changes of -9.1%, -10.1%, and -4.5% respectively). There was also an increase in blood urea nitrogen (BUN) with both canagliflozin arms compared to placebo. The reductions in eGFR and increased BUN with canagliflozin arms occurred early and trended back towards

baseline by week 26. A lower proportion of patients treated with canagliflozin 100 and 300 mg had a progression of albuminuria from baseline to week 26 compared to placebo (5.1, 8.3, and 11.8% respectively). Lastly, treatment with canagliflozin 100 and 300 mg was associated with greater median percent reductions in UACR from baseline to week 26 compared to placebo (-29.9%, -20.9%, and -7.5%, respectively), although no statistical significance was calculated.

As a follow-up extension study, 229 of the 269 patients that completed the first 26 weeks of therapy continued for an additional 26 weeks to evaluate the efficacy and safety of canagliflozin at week 52.<sup>13</sup> At week 52, changes in A1C from baseline were numerically lower for canagliflozin 100 mg vs. placebo (-0.19% vs. 0.07%) and canagliflozin 300 mg vs. placebo (-0.33% vs. 0.07%). Confidence intervals (95% CI) for calculated differences between canagliflozin 100 mg and 300 mg showed that only canagliflozin 300 mg significantly reduced A1C from baseline to week 52. Similar to changes in FPG from the 26-week study, changes at 52 weeks were numerically lower with both doses of canagliflozin but did not achieve statistical significance. Decreases in eGFR at week 52 were seen with canagliflozin 100 and 300 mg compared with placebo (-2.1, -4.0 and -1.6 ml/min/1.73m<sup>2</sup>, respectively). Assessing changes in UACR from baseline to week 52 showed that placebo was associated with a 19.7% increase in UACR, compared to a -16.4% decrease with canagliflozin 100 mg and -28.0% with canagliflozin 300 mg. Similar to the results seen at the 26-week time period, the proportion of patients progressing from normal UACR to albuminuria was lower with canagliflozin 100 and 300 mg (10.3%, 14.7%, respectively) compared to placebo (17.1%). These two trials provide evidence that canagliflozin is associated with a clinically relevant A1C reductions, and the potential to

improve UACR in patients with T2DM and CKD who require additional glucose-lowering therapy.

The most recent study of canagliflozin in patients with T2DM and CKD was a secondary analysis of a previous multicentered clinical trial of patients randomized to either canagliflozin 100 or 300 mg daily or glimepiride titrated up to 8 mg daily. Data for a subgroup of patients (n=230) with UACR  $\geq 30$  mg/g at baseline was reported separate from the overall study cohort. Baseline characteristics for the CKD subgroup were similar to the overall study group. Mean age ranged from 55.6 to 58.5 years, and baseline A1C was 7.9% in patients randomized to glimepiride or canagliflozin 100 mg, and 8.0% in the canagliflozin 300 mg group. Mean eGFR at baseline ranged from 86.5 to 91.1 ml/min/1.73m<sup>2</sup>, similar to the overall study population. Mean UACR varied between the study groups of the CKD patients, with the lowest UACR (56.5 mg/dL) in canagliflozin 100 mg group and the highest UACR value (75.2 mg/dL) in the canagliflozin 300 mg group. Endpoints reported separately for this subgroup of CKD patients included 30% decline in eGFR and percent reduction in UACR over a 2-year period. No data on A1C-lowering between glimepiride and canagliflozin groups were reported for the CKD subgroup. However, in the CKD subgroup, significant reductions in UACR from baseline were reported with canagliflozin 100 mg (-31.7%; P=0.01) and canagliflozin 300 mg (-49.3%; p<0.001) versus glimepiride. Additionally, decline in eGFR was measured during the 2-year trial period. In patients with baseline UACR >30 mg/g, calculated hazard ratios (HR) for 30% eGFR decline were lower for canagliflozin 100 mg (HR=0.37; p=0.03) and canagliflozin 300 mg (HR=0.69; p=0.33)

versus glimepiride. This trial provides evidence that canagliflozin may be more effective in slowing progression of DN compared to glimepiride.

Currently, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) clinical trial is prospectively evaluating renal and cardiovascular endpoints with canagliflozin vs placebo in patients with T2DM and CKD stage 2 or 3 with UACR >300 mg/g, already treated with maximally tolerated ACE-i or ARB. (NCT02065791). This trial's primary composite endpoint is time to first occurrence of end-stage kidney disease (ESKD), doubling of serum creatinine, renal or cardiovascular death. Expected trial duration is 5.5 years.<sup>18</sup>

### **Relevance to Patient Care and Clinical Practice**

Current standard of care for preventing progression of CKD includes controlling BP and glucose, as well as use of renin-angiotensin inhibitors. Several oral and injectable antihyperglycemic agents are available to improve glucose in patients with T2DM. Current standards of care promote a patient-centered approach when selecting additional glucose-lowering medication, considering risk of hypoglycemia, weight gain, adverse effects, and most recently cardiovascular and renal effects.<sup>5</sup> Cardiovascular outcomes trials have reported reduced cardiovascular risk with liraglutide, canagliflozin, and empagliflozin and reported positive changes in composite renal endpoints, although in a predominately non-CKD population. Whether the cardiovascular

or renal benefits of these medications translate to patients with CKD has not been prospectively evaluated in long-term clinical trials.

Our literature review identified eight studies that reported efficacy and/or assessment of renal changes in patients with CKD and T2DM. Available studies suggest that in patients with CKD, both GLP-1RA and SGLT2-I are associated with A1C reductions similar to patients without CKD. A recent meta-analysis of 38 randomized controlled trials including nearly 24,000 patients with T2DM treated with one of three SGLT2-I (canagliflozin, dapagliflozin, or empagliflozin) reported significant A1C reductions of -0.6% to -0.9%, compared to placebo.<sup>19</sup> Similarly, a meta-analysis of available GLP-1RA included 34 trials and over 14,000 patients with T2DM reported that GLP-1RA have the ability to lower A1C -0.55% to -1.21% versus placebo.<sup>20</sup> From our review, there is evidence that liraglutide and several SGLT2-I positively impact albuminuria either by reducing UACR in patients with micro- or macroalbuminuria, or by preventing progression to albuminuria. Both liraglutide and the SGLT2-I studied produce a small decrease in eGFR compared to baseline, which may not be clinically significant. This small decrease in eGFR would likely be outweighed by the positive renal effects of preventing or reversing albuminuria.

The precise mechanism by which SGLT2-I and GLP-1RA exert their potentially renoprotective benefits is currently unknown. Potential mechanisms for improving albuminuria may be multifactorial, including: increased natriuresis, reduced intraglomerular pressure, reduced renal hyperfiltration, as well as pleiotropic effects such as anti-inflammatory effects.<sup>21,22</sup> Both antihyperglycemic classes have been shown to inhibit a sodium-hydrogen exchanger protein

(NHE3) located in the proximal tubule, which may be responsible for the natriuretic effect and excreting excess sodium.<sup>21,22</sup> While tight glucose control is associated with reduced risk for developing diabetic nephropathy, it is unlikely that the renal benefits of SGLT2-I and GLP-1RA are entirely due to glucose lowering. Studies as short as 26 weeks demonstrated improvements in albuminuria despite minimal A1C reductions. Even in long-term CVOT, the improvement in glycemic control was modest, and not likely to be the sole contributor to improving renal outcomes or reducing cardiovascular risk. While both GLP-1RA and SGLT2-I are also associated with reductions in body weight and BP, these effects are modest and may not fully explain the cardiovascular and renal benefits seen reported in our review. Perhaps the culmination of reduced glucose, BP, natriuresis, and anti-inflammatory effects lead to the observed improvements in albuminuria.

Regardless of the mechanism, these agents have demonstrated glucose-lowering and improved albuminuria effects in patients with T2DM and CKD. Additionally, long-term CVOTs trials have reported reduced cardiovascular risk in patients at high risk of cardiovascular disease. While not without potential adverse effects, we believe that GLP-1RA and SGLT2-I should become first-line agents (in addition to renin-angiotensin inhibitors) in patients with T2DM and CKD, a population at increased risk for CV mortality. Ongoing clinical trials prospectively evaluating SGLT2-I will provide definitive information regarding renoprotective benefits in patients with T2DM and CKD, already receiving standard of care. A meta-analysis of available data assessing positive albuminuria changes effects of SGLT2-I and GLP-1RA would be a valuable endeavor.

## Conclusion

Our review highlights that both SGLT2-I and GLP-1RA can be used in patients with T2DM and CKD to improve glycemic control. Three SGLT2-I and the GLP-1RA liraglutide reduced A1C and improved or prevented albuminuria in patients with CKD and T2DM. Current ADA standards now recommend consideration of renal effects when choosing antihyperglycemic therapy in patients with T2DM and note benefits of three agents on progression to diabetic nephropathy. Prospective trials are needed to confirm the observed renoprotective effects in patients with CKD and T2DM. If future trials are successful, SGLT2-I and/or GLP-1RA should join renin-angiotensin inhibitors as recommended treatment in patients with uncontrolled T2DM and CKD to slow progression of diabetic kidney disease.

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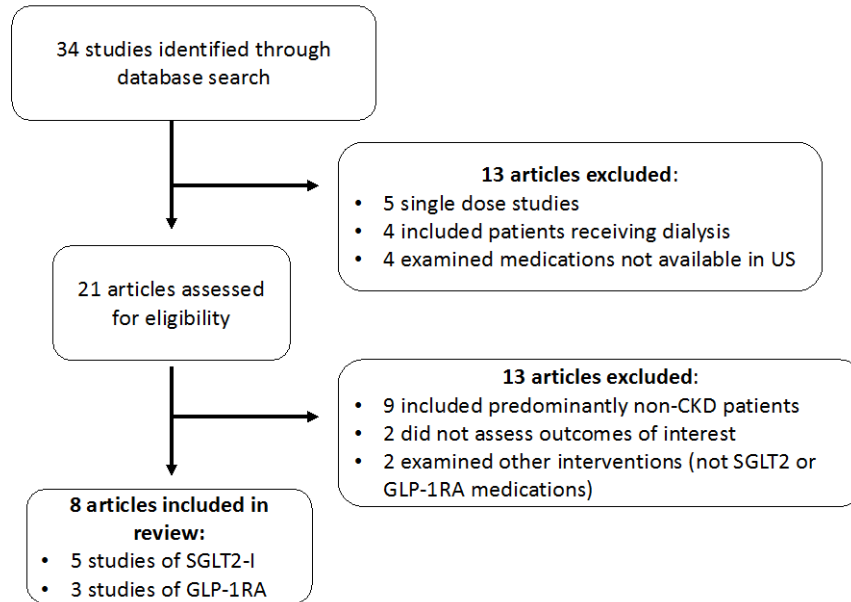
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<b>Table 1: Renal dose adjustments for antihyperglycemic agents</b>		
<b>Biguanides</b>		
Metformin	eGFR 30-44	Do not initiate Consider 50% dose reduction if previously treated
	eGFR <30	Use is contraindicated
<b>DPP4-inhibitors</b>		
Alogliptin	CrCl ≥30-59	12.5 mg daily
	CrCl ≥15-29	6.25 mg daily
	ESRD (CrCl <15 or requiring hemodialysis)	6.25 mg daily
Saxagliptin	eGFR <45	2.5 mg daily
	ESRD requiring hemodialysis	2.5 mg daily
Sitagliptin	eGFR ≥30-44	50 mg daily
	eGFR <30	25 mg daily
	ESRD requiring hemodialysis or peritoneal dialysis	25 mg daily
<b>SGLT2-Inhibitors</b>		

Canagliflozin	eGFR 45-59	100 mg daily (maximum dose)
	eGFR $\geq$ 30-44	Do not initiate Discontinue if eGFR persistently <45
	eGFR<30	Use is contraindicated
Dapagliflozin	eGFR 30-59	Do not initiate Discontinue if eGFR persistently <60
	eGFR <30	Use is contraindicated
Empagliflozin	eGFR 30-44	Do not initiate Discontinue if eGFR persistently <45
	eGFR<30	Use is contraindicated
Ertugliflozin	eGFR 30-59	Do not initiate Discontinue if eGFR persistently <60
	eGFR <30	Use is contraindicated
<b>GLP-1 receptor agonists</b>		
Exenatide	CrCl <30 or ESRD	Use not recommended
Lixisenatide	eGFR <15	Use not recommended
<b>Alpha-glucosidase inhibitor</b>		
Acarbose	eGFR <30	Use not recommended
Miglitol	eGFR <25	Use not recommended
CrCl= creatinine clearance (ml/min); eGFR= estimated glomerular filtration rate (ml/min/1.73m <sup>2</sup> ); ESRD = end-stage renal disease.		

Figure 1: Study selection flowchart



**Table 2: Summary of trials of GLP-1 Receptor agonists and SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease**

Study	Study design	Number of pts	Baseline renal function (eGFR- mL/min/1.73m <sup>2</sup> ) or UACR)	Study duration	Treatment groups	Efficacy (change in A1C)	Renal endpoints assessed
<b>GLP1 Receptor Agonists</b>							
Davies et al. 2016	Randomized, double-blind, and placebo-controlled trial	279	<b>Baseline eGFR:</b> Liraglutide: 45.4 ml/min/1.73m <sup>2</sup>  Placebo: 45.5 ml/min/1.73m <sup>2</sup>  <b>Baseline UACR:</b>	26 weeks	Liraglutide titrated up to 1.8 mg daily versus placebo	<b>Change in A1C from baseline to week 26:</b> Liraglutide vs placebo: (-1.05% vs. -0.38%; p<0.0001)	<b>Estimated ratio of eGFR at week 26 to baseline:</b>  Liraglutide and placebo (0.99 vs. 1.01; p=0.36)

			Liraglutide: 55.5 mg/g Placebo: 69.8 mg/g			<b>Change in FPG (mg/dL) from baseline to week 26:</b>  Liraglutide vs. placebo (-22.0 vs. -10.3; p=0.036)	<b>Estimated ratio of UACR at week 26 to baseline:</b>  Liraglutide and placebo (0.87 vs. 1.05; p=0.19)
Imamura, et al. 2013	Non-randomized, Single arm	23	<b>Baseline eGFR:</b> 58.2 ml/min/1.73m <sup>2</sup>  <b>Baseline UPCR:</b> 2.53 g/g	12 months	Liraglutide 0.3mg/d titrated up to 0.9 mg/d	<b>Change in A1C from baseline to 12 months:</b> 7.4% to 6.9% (p=0.035).	Change in annual eGFR decline (ml/min/1.73m <sup>2</sup> ) before and after 12 months treatment:  -6.6 to -0.33 (p=0.003)



							Change in urinary protein (g/g Cr) from baseline to 12 months: 2.53 to 1.47 (p=0.0015)
Bouchi, et al. 2017	Single-center, randomized, open-label, comparative trial	17	All patients had eGFR >60, but UACR >200 mg/g at baseline:  Liraglutide: 220 mg/g Control: 254 mg/g	36 weeks	Insulin treatment (control) vs. insulin + liraglutide 0.3 mg/d	Change in A1C from baseline to week 24: liraglutide vs. control (-0.7% vs. +0.2%; p=0.035)	<b>Change in UACR from baseline to week 24:</b>  liraglutide vs. control

					titrated to 0.9 mg/d (liraglutide)		(-129 mg/g vs. +56 mg/g; p=0.016)
<b>SGLT2 inhibitor trials</b>							
Kohan et al. 2014	Randomized, double- blind, placebo- controlled trial	252  (139 completed 104 weeks of extension period)	Baseline eGFR 30-59 ml/min/1.73m <sup>2</sup> in 91.7% of all study patients  <b>Baseline UACR:</b> Dapagliflozin (5 or 10 mg): 73-79 mg/g Placebo: 67 mg/g	24 weeks (some patients completed up to 104 weeks)	Dapagliflozin 5 or 10 mg vs. placebo	<b>Change in A1C from baseline to week 24:</b>  Dapagliflozin 5 mg vs. placebo (-0.41% vs. -0.32%; p=0.561)  Dapagliflozin 10 mg vs. placebo (-0.44% vs. -0.32%; p=0.435)	<b>Mean change in eGFR (ml/min/1.73m<sup>2</sup>) from baseline to week 24:</b> (No p- value reported)  Dapagliflozin 5 mg vs. placebo (-2.38 vs. -0.25)

						<p>Dapagliflozin 10 mg vs. placebo (-4.80 vs. -0.25)</p> <p><b>Change in FPG (mg/dL) from baseline to 24 weeks:</b> (No p-value reported):</p> <p>Dapagliflozin 5 mg vs. placebo (-5.2 vs. 8.4)</p>	<p>Dapagliflozin 10 mg vs. placebo (-4.80 vs. -0.25)</p> <p><b>Proportion of patients experienced UACR &gt;1800 mg/g during 104-week treatment period:</b> (No p-value reported)</p> <p>Dapagliflozin 5 mg (10.8%)</p> <p>Dapagliflozin 10 mg</p>
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						Dapagliflozin 10 mg vs. placebo (-0.6 vs. 8.4)	(9.5%) Placebo (13.3%)  <b>Number of patients shifting to lower UACR category at week 104:</b> Dapagliflozin: 22.6% Placebo: 10.7%
Yale et al. 2013	Randomized, double-	269	<b>Baseline eGFR:</b> 39.4 ml/min/1.73m <sup>2</sup>	26 weeks	Canagliflozin 100 or 300		

<p>blind, placebo- controlled trial</p>		<p><b>Baseline UACR:</b> 30.0 mg/g</p>		<p>mg vs. placebo</p>	<p><b>Change in A1C from baseline to week 26:</b>  Canagliflozin 100 mg vs. placebo (-0.33% vs. -0.03%; p&lt;0.05)  Canagliflozin 300 mg vs. placebo (-0.44% vs. -0.03%; p&lt;0.001)</p>	<p><b>Change in eGFR (ml/min/1.73m<sup>2</sup>) from baseline to week 26:</b> (No p-value reported)  Canagliflozin 100 mg vs. placebo (-3.6 vs. -1.4)  Canagliflozin 300 mg vs. placebo (-3.9 vs. -1.4)</p>
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						<b>Change in FPG (mg/dL) from baseline to week 26:</b>	<b>Percent reduction in UACR from baseline to week 26:</b>
						Canagliflozin 100 mg vs. placebo (-11.7 vs. 0.5; p=NS)	(No p-values reported)  Canagliflozin 100 mg vs. placebo (-29.9% vs. -7.5%)
						Canagliflozin 300 mg vs. placebo (-14.9 vs. 0.5; p=NS)	Canagliflozin 300 mg vs. placebo (-20.9% vs. -7.5%)

							<p><b>Proportion of patients progressing from normal UACR to albuminuria from baseline to week 26:</b> (No p-value reported)</p> <p>Canagliflozin 100 mg (5.1%)</p> <p>Canagliflozine 300 mg (8.3%)</p> <p>Placebo (11.8%)</p>
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Yale et al. 2014	Extension of Yale et al. 2013 study	229	<b>Baseline eGFR:</b> 39.4 ml/min/1.73m <sup>2</sup>  <b>Baseline UACR:</b> 30.0 mg/g	52 weeks (26-week extension of previous Yale et al. 2013 study)	Canagliflozin 100 or 300 mg vs. placebo	<b>Change in A1C from baseline to week 52:</b>  Canagliflozin 100 mg vs. placebo (-0.19% vs. 0.07%; 95% CI, -0.53 to 0.001)  Canagliflozin 300 mg vs. placebo (-0.33% vs. 0.07%; 95% CI, -0.68 to - 0.14)	<b>Change in eGFR (ml/min/1.73m<sup>2</sup>) from baseline to week 52:</b>  Canagliflozin 100 mg vs. placebo (-2.1 vs. -1.6; 95% CI, -2.8 to 1.7)  Canagliflozin 300 mg vs. placebo (-4.0 vs. -1.6; 95% CI, -4.6 to -0.3)
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						<b>Change in FPG (mmol/L) from baseline to week 52:</b>	<b>Percent change in UACR from baseline to week 52:</b>  (No p-value reported)
						Canagliflozin 100 mg vs. placebo (-0.1 vs. 0.5; 95% CI, -1.5 to 0.2)	Canagliflozin 100 mg vs. placebo (-16.4% vs. 19.7%)
						Canagliflozin 300 mg vs. placebo (-0.3 vs. 0.5; 95% CI, -1.7 to 0.1)	Canagliflozin 300 mg vs. placebo (-28.0% vs. 19.7%)

							<p><b>Proportion of patients progressing from normal UACR to albuminuria from baseline to week 52:</b></p> <p>Canagliflozin 100 mg (10.3%)</p> <p>Canagliflozine 300 mg (14.7%)</p> <p>Placebo (17.%)</p>
Heerspink et al. 2017	Secondary analysis of patients	230	<p><b>Baseline eGFR:</b></p> <p>86.5-91.1 ml/min/1.73m<sup>2</sup></p>	2 years	Canagliflozin 100 or 300 mg vs.	<b>Change in A1C for subgroup with UACR</b>	<b>Hazard ratio (HR) for 30% decline in eGFR</b>

<p>with UACR ≥30 mg/g enrolled in previous randomized trail</p>		<p><b>Baseline UACR:</b></p> <p>Canagliflozin 100 mg: 56.5 mg/g</p> <p>Canagliflozin 300 mg: 75.2 mg/g</p> <p>Glimepiride: 60.1 mg/g</p>		<p>glimepiride titrated up to 8 mg</p>	<p><b>≥30 mg/g not reported</b></p>	<p><b>(canagliflozin vs. glimepiride):</b></p> <p>Canagliflozin 100 mg: HR=0.37; p=0.03</p> <p>Canagliflozin 300 mg: HR=0.69; p=0.33</p> <p><b>Percent reduction in UACR (canagliflozin vs. glimepiride):</b></p> <p>Canagliflozin 100 mg:</p>
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							-31.7% (p=0.01)  Canagliflozin 300 mg: -49.3% (p<0.001)
Barnett et al. 2014	Randomized, double-blind, placebo-controlled trial  Included subgroups of patients	374 patients with CKD stage 3	<b>Baseline eGFR</b> (Stage 3 CKD patients): 44.9 ml/min/1.73m <sup>2</sup>	52 weeks	Empagliflozin 25 mg or placebo	<b>Change in A1C from baseline to week 24:</b>  Empagliflozin vs. placebo (-0.37% vs. 0.05; p<0.0001)  <b>Change in A1C from baseline to week 52:</b>	<b>Change in UACR (mg/g) from baseline to week 52:</b>  Empagliflozin vs. placebo (-183.8; p=0.0031);

	with CKD 2-4  (subgroup analysis available for each CKD stage)					Empagliflozin vs. placebo  (-0.32% vs. 0.12; p<0.0001)  <b>Change in FPG (mmol/L) from baseline to week 24:</b>  Empagliflozin vs. placebo  (-0.5 vs. 0.6; p<0.0001)	<b>Proportion of patients progressing from normal UACR to microalbuminuria:</b>  (No p-value reported)  Empagliflozin vs. placebo (12.2% vs. 22.2%)  <b>Proportion of patients progressing from microalbuminuria to macroalbuminuria:</b>
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						<p><b>Change in FPG (mmol/L) from baseline to week 52:</b></p> <p>Empagliflozin vs. placebo (-0.4 vs. 0.3; p=0.0037)</p>	<p>(No p-value reported)</p> <p>Empagliflozin vs placebo (2.0% vs. 11.4%)</p>
<p>A1C= hemoglobin A1C; CKD= chronic kidney disease; eGFR= estimated glomerular filtration rate; FPG= fasting plasma glucose; UACR= Urinary albumin-to-creatinine ratio; UPCR= Urine protein-to-creatinine ratio</p>							