Therapeutic Considerations for Antihyperglycemic Agents in Diabetic Kidney Disease

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ABSTRACT

Diabetic kidney disease is among the most frequent complications of diabetes, with approximately 50% of patients with ESRD attributed to diabetes in developed countries. Although intensive glycemic management has been shown to delay the onset and progression of increased urinary albumin excretion and reduced GFR in patients with diabetes, conservative dose selection and adjustment of antihyperglycemic medications are necessary to balance glycemic control with safety. A growing body of literature is providing valuable insight into the cardiovascular and renal safety and efficacy of newer antihyperglycemic medications in the dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, and sodium-glucose cotransporter 2 inhibitor classes of medications. Ongoing studies will continue to inform future use of these agents in patients with diabetic kidney disease.


The United Nations General Assembly has recognized diabetes mellitus (DM) as a condition of major global concern in recognition of the growing numbers of people with DM and the tremendous effect of this disease on health worldwide.1 In 2015, an estimated 415 million people worldwide had DM, with a projected increase to 642 million by the year 2040.2 Notably, these figures include a disproportionately large number of individuals in low- to middle-income countries.3 Similar to the global trends, the prevalence of DM among adults in the United States increased from 10% from 1988 to 1994 to an estimated 12% from 2011 to 2012.4 Approximately 30% of those with type 1 DM and 40% of those with type 2 diabetes mellitus (T2DM) develop diabetic kidney disease (DKD).5 Adults with DM are at 1.5-fold higher risk of all-cause death compared with those without DM, and the risk is greatly amplified among those with DKD.6,7 Prevention of diabetic microvascular complications, particularly DKD, by long-term intensive glycemic control is well established for both type 1 DM and T2DM.8,9 Optimizing glycemic control in this population, however, is complicated by alterations in the kidneys’ role in maintaining glucose homeostasis, increased risk of hyperglycemia, and alterations in the pharmacokinetics of antihyperglycemic agents.10

This review will provide a discussion of challenges associated with glycemic management in patients with DKD. Additionally, considerations for the use of antihyperglycemic agents in patients with DKD will be discussed, including findings from cardiovascular outcome trials (CVOTs) recently reported with newer agents approved for the treatment of DM.

DIABETES MANAGEMENT: CHALLENGES IN THE SETTING OF DKD

Kidneys and Glucose Homeostasis

Under physiologic circumstances, the kidneys play a significant role in glucose homeostasis via (1) gluconeogenesis, (2) reabsorption of glucose from the glomerular filtrate, and (3) uptake of glucose from the circulation to satisfy its own metabolic needs.11 An estimated 20%–25% of glucose released into the circulation during the postabsorptive (fasting) state originates from gluconeogenesis in the kidneys.11,12 Interestingly, renal gluconeogenesis increases in the postprandial state and accounts for approximately 60% of endogenous glucose release during this time, which has been hypothesized as a function to facilitate replenishment of glycogen stores in the liver.11,12 Approximately 160–180 g/d filtered glucose is reabsorbed from the
glomerular filtrate primarily in the proximal convoluted tubule via the sodium-glucose cotransporter type 2 (SGLT-2).\textsuperscript{12,13} The remaining glucose reabsorption from the glomerular filtrate is achieved via SGLT-1 transporters in the straight segment of the descending proximal tubule\textsuperscript{12,13} as illustrated in Figure 1.

In DM, both postabsorptive gluconeogenesis and glomerular filtration of glucose are increased. Notably, gluconeogenesis by the kidney is comparable with that of the liver (2.6 and 2.2 μM/kg per minute, respectively).\textsuperscript{11} The amount of glucose filtered into the urine increases in a linear manner with increasing plasma glucose concentrations. As an adaptive response to this increase, there is an amplified expression of SGLT-2 transporters resulting in a raised set point for urinary glucose secretion.\textsuperscript{14,15} Metabolic derangements seen in DM, including hyperglycemia and hyperaminoacidemia, contribute to renal hemodynamic changes of glomerular hyperfiltration that culminate in injury leading to structural changes typical of DKD (Figure 2).\textsuperscript{16}

Hypoglycemia Risk
Patients with diabetes and impaired kidney function are at increased risk for hypoglycemic events. A retrospective cohort analysis of nearly 244,000 patients with and without DM showed a higher frequency of hypoglycemic events in patients with chronic kidney disease (CKD) (defined by an eGFR < 60 ml/min per 1.73 m\textsuperscript{2}) when compared with those without CKD.\textsuperscript{17} Among patients with DM, the rate of hypoglycemia (blood glucose < 70 mg/dl) was 11/100 versus 5/100 patient-mo among patients with and without CKD, respectively.\textsuperscript{17} A post hoc analysis of 3700 participants from the Action to Control Cardiovascular Risk in Diabetes Trial who met criteria for CKD stages 1–3 showed that intensive glucose lowering to a glycated hemoglobin (HbA1C) < 7% was associated with both an approximately 30% higher all-cause mortality (1.306; 1.065–1.600) and a 40% higher cardiovascular (CV) mortality (1.42; 1.052–1.892).\textsuperscript{18} Among patients with CKD, intensive glucose lowering was associated with higher rates of hypoglycemic episodes requiring assistance when compared to those in the standard treatment group (22% versus 9%, respectively).

In the setting of advanced CKD, another loss of function performed by the kidney is lower capacity for gluconeogenesis and release of glucose into blood, thus placing patients at increased risk for hypoglycemia.\textsuperscript{17} Another contributor to the increased risk of hypoglycemia in people with DKD is altered metabolism and elimination of glucose-lowering medications.\textsuperscript{19} For example, exogenous insulin is normally metabolized by the kidney and thus, exhibits a prolonged half-life in patients with CKD. Similarly, decreased clearance of many other anti-hyperglycemic agents results in prolonged exposure to higher drug levels, requiring dose de-escalation for many agents.\textsuperscript{19}

Glycemic Monitoring in CKD
HbA1C is the gold standard biomarker of glycemic control, but this measure has noteworthy limitations related to precision and interpretation in the DKD population.\textsuperscript{20} A prospective cohort study assessed the relationship between HbA1C and blood glucose in various stages of CKD, including ESRD. After up to 10 years of follow-up, there was a strong inverse relationship between HbA1C and declining kidney function. However, later CKD stage modified the relationship between HbA1C and blood glucose, such that there was a bias to the low. In general, HbA1C measures lower at given levels of ambient
Glycemia in patients with advanced CKD (stages 3b–5, including those treated by dialysis). Factors associated with increased red blood cell turnover (e.g., shortened red blood cell lifespan, decreased erythropoiesis, blood transfusions, and treatment with iron or erythropoiesis-stimulating agents [ESAs]) also lowers the HbA1C relative to ambient blood glucose. Indeed, use of ESAs was identified as a key risk factor for low HbA1C relative to ambient blood glucose. Additionally, use of ESAs was identified as a key risk factor for low HbA1C relative to ambient blood glucose. However, this effect is now uncommon with current standardized HbA1C assays.

Several other markers of glycemic control, such as glycated albumin, glycated fructosamine, and 1,5-anhydroglucitol, are under study. To date, there are no prodigious data or assay validation to support clinical use of these alternative glycemic markers over HbA1C. Despite the inherent limitations of HbA1C measurement, it remains a key biomarker for glycemic management in people with DM and CKD. Self-monitoring of blood glucose (SMBG) provides crucial information about glycemic control and daily fluctuations. Continuous glucose monitoring holds promise for daily glycemic assessment but remains to be validated in patients with CKD.

Guideline-recommended HbA1C goals for patients with DM and CKD have been informed by a series of several landmark studies. The Diabetes Control and Complications (DCCT) Trial and the United Kingdom Prospective Diabetes Study (UKPDS) in early-stage T1DM and T2DM, respectively, showed beneficial effects of intensive glycemic control on development of heart disease and microvascular complications.

Figure 2. Metabolic derangements present in diabetes contribute to renal hemodynamic changes of glomerular hyperfiltration. (A) Normal glomerulus. The balance between vasodilation and vasoconstriction in the afferent (upstream) and efferent (downstream) arterioles determines intraglomerular pressure, a major regulator of GFR. Distal tubular delivery of solute, particularly sodium chloride, at the macula densa regulates afferent arteriolar tone via tubuloglomerular feedback. (B) Glomerulus in diabetes. The afferent arteriole opens in response to vasodilatory factors, such as hyperglycemia and high blood levels of amino acids. Because of a high filtered load of glucose, reabsorption of glucose and sodium chloride is increased in the proximal tubule. The afferent arteriole also dilates in response to decreased delivery of sodium chloride to the distal tubular macula densa via tubuloglomerular feedback. The efferent arteriole vasoconstricts in response to high local production of angiotensin II. Overall, the balance shifts to glomerular hyperfiltration as a result of high intraglomerular pressure from afferent arteriolar vasodilation and efferent vasoconstriction. Reprinted from ref. 16, with permission.
Update on Use of Conventional Antihyperglycemic Agents in Diabetes and CKD

Metformin
In the year 2016, the US Food and Drug Administration (FDA) revised warnings regarding the use of metformin in patients with DKD.37 Revisions made to the prescribing information for metformin-containing products included indicating that metformin may be safely used in patients with mild to moderate “renal impairment” and recommending that serum creatinine-based eGFR be used as the standard measure of kidney function for metformin dose adjustments as opposed to serum creatinine, such as was previously recommended.37 This labeling change represents the first time that the FDA has amended their recommendations for the use of metformin in CKD since the drug was approved in the United States in 1995 (Table 3).37

Of note in the revised labeling, metformin should still be used cautiously in patients with heart failure or liver disease and during acute illness and/or instances of tissue hypoxia, where the risk of lactic acid accumulation is increased.39,40 However, a recent systematic review of metformin use in patients with moderate to severe DKD with congestive heart failure or chronic liver disease with associated hepatic impairment showed that metformin use was associated with reduced all-cause mortality.41 Specific clinical data on the risk of metformin-associated lactic acidosis in patients with DKD are limited, with current evidence suggesting that the overall risk is low.40

Insulin
In contrast to endogenously secreted insulin, which undergoes substantial degradation in the liver, exogenous insulin is to a larger degree eliminated by the kidneys.42 Insulin is filtered at the glomerulus followed by reabsorption in the proximal tubule. There is also uptake and degradation of insulin by peritubular endothelial cells.43 Insulin clearance decreases in parallel with a decrease in GFR, leading to an overall decrease in exogenous insulin requirements.44,45 Because specific insulin preparations have not been well studied in CKD and because individual patient needs vary substantially, no definitive guidelines exist for insulin dose adjustments on the basis of eGFR. Because of the lack of evidence for many of the oral and noninsulin injectable antihyperglycemic agents, however, insulin therapy is a mainstay of therapy in patients with CKD. It is essential that blood glucose levels be monitored closely and that insulin doses be individualized on the basis of each patient’s glycemic response and patterns, with a mindful approach to titration to minimize the risk of hypoglycemic events in this high-risk population.

Sulfonylureas and Meglitinides
Hypoglycemia is consistently a primary treatment concern with the sulfonylurea and meglitinide classes of medications but assumes particular importance in the setting of CKD.19 Glyburide is extensively metabolized in the liver into several active metabolites that are excreted by the kidney and is not recommended for use in DKD.33,46 Glimepiride is associated with less hypoglycemia when compared with glyburide and should

ANTIHYPERTHYROGLYCEMIC MEDICATIONS: CONSIDERATIONS IN THE SETTING OF CKD

Despite lingering uncertainties concerning glycemic monitoring and adjustment of targets, glycemic management and CV risk reduction remain essential cornerstones of DM management in patients with CKD. Given the increased risk for hypoglycemia and potential for altered metabolism and kidney clearance of antihyperglycemic drugs, prudent use of available agents is appropriate. Table 2 provides a summary of dosing recommendations for noninsulin therapies currently available in the United States in patients with DM and CKD.19,37,38

Table 1. Select glycemic target recommendations for patients with DKD

<table>
<thead>
<tr>
<th>Guideline/Consensus Report</th>
<th>Recommendations/Suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA standards of medical care in diabetes 201726</td>
<td>Less stringent HbA1C goals (such as &lt;8%) may be appropriate for patients with advanced complications, including CKD</td>
</tr>
<tr>
<td>DKD: a report from an ADA consensus conference19</td>
<td>HbA1C&lt;8% when GFR&lt;60 ml/min per 1.73 m² due to increased hypoglycemia risk</td>
</tr>
<tr>
<td>KDOQI clinical practice guideline for diabetes and CKD: 2012 update33</td>
<td>Reliance on SMBG in making treatment decisions due to imprecision of HbA1C</td>
</tr>
<tr>
<td></td>
<td>Recommend not treating to an HbA1C of &lt;7.0% in patients at risk of hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Suggest that target HbA1C be extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia, such as those with CKD</td>
</tr>
</tbody>
</table>

ADA, American Diabetes Association; KDOQI, Kidney Disease Outcomes Quality Initiative.
be initiated at a low dose and titrated conservatively if used (refer to Table 2). Glipizide, in contrast, is metabolized by the liver into several inactive metabolites, and its clearance and elimination half-life are not affected by a reduction in eGFR. Accordingly, dose adjustments in patients with CKD are not necessary with glipizide, making it the sulfonylurea of choice in this population.

Similarly, the main concern with meglitinide use in the setting of CKD is...
Metformin should be discontinued in patients with History of liver disease, alcoholism, or heart failure.33,52 This medication class.33,52 fracture risk that have been observed with BP, congestive heart failure, and increased cerns of refractory avoided in the setting of DKD due to con-

Table 2, thiazolidinedione use is generally avoided in the setting of DKD due to con-
cerns of refractory fluid retention, higher BP, congestive heart failure, and increased fracture risk that have been observed with this medication class.33,52

Thiazolidinediones
Both pioglitazone and rosiglitazone are nearly completely metabolized by the liver.49–51 Despite the lack of a need for dosage adjustments in patients with DKD (Table 2), thiazolidinedione use is generally avoided in the setting of DKD due to concerns of refractory fluid retention, higher BP, congestive heart failure, and increased fracture risk that have been observed with this medication class.33,52

Considerations for Use of Newer Antihyperglycemic Agents in CKD
In the year 2008, the US FDA issued guidance for industry outlining expectations for evaluating CV risk in new antihyperglycemic therapies seeking approval for the treatment of T2DM.53 Accordingly, several agents in the following antihyperglycemic classes have pending and/or available data pertaining to CV and kidney outcomes from dedicated CVOTs.

Dipeptidyl Peptidase-4 Inhibitors
All of the currently available dipeptidyl peptidase-4 (DPP-4) inhibitors are labeled for use in CKD, but sitagliptin, saxagliptin, and alogliptin require downward dose titration on the basis of eGFR.54 Linagliptin, in contrast, does not require dose adjustment on the basis of kidney function.55 DPP-4 inhibitors have been shown to lower HbA1C by approximately 0.3% in patients with CKD stages 3 and 4 (−0.52%; 95% confidence interval [95% CI], −0.64 to −0.39).56 A potential renal sparing effect, as noted by a reduction in albuminuria with treatment, has been seen with all of the currently available DPP-4 inhibitors.57–60 Whether effects on albuminuria are independent of changes in BP or glycemic changes is unknown.

Data from several CVOTs involving DPP-4 inhibitors have been reported (Table 4).61–67 The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) showed that sitagliptin was noninferior to placebo for the primary composite CV outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina (hazard ratio [HR], 0.98; 95% CI, 0.88 to 1.09; P<0.001).64 Sitagliptin was additionally shown to have no clinically significant effect on CV or CKD outcomes, irrespective of baseline eGFR, in another TECOS analysis.62 Likewise, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) Trial reported noninferiority for saxagliptin when compared with placebo on the primary composite outcome (HR, 1.00; 95% CI, 0.89 to 1.12; P<0.001).65 In an assessment of kidney outcomes from the SAVOR-TIMI 53 Trial cohort, treatment with saxagliptin was associated with an improvement or less deterioration in albumin-to-creatinine ratio categories from baseline to the end of the trial (for participants with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria).64 Improvements in albumin-to-creatinine ratio were observed in the absence of an effect on eGFR and were not explained by improvements in glycemic parameters alone. The SAVOR-TIMI 53 Trial reported an increase in hospitalization for heart failure with saxagliptin when compared with placebo (HR, 1.27; 95% CI, 1.07 to 1.51; P=0.01).67 In response to these findings, a meta-analysis of randomized clinical trials of DPP-4 inhibitors was conducted showing the overall risk of acute heart failure to be higher in patients treated with DPP-4 inhibitors versus those treated with placebo or an active comparator.68 However, this observation was not externally validated by analysis of congestive heart failure admissions in clinical practice on the basis of “real world” large administrative datasets from Canada, the United Kingdom, and the United States.69 Several ongoing DPP-4 inhibitor trials will soon provide additional data related to health outcomes with these agents in patients with DKD. The Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin Study and the Renal Effects of DPP-IV Inhibitor Linagliptin in Type 2 Diabetes Study are investigating potential for “renoprotective” effects of these agents.70,71

Glucagon-Like Peptide-1 Receptor Agonists
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) mimic the action of

<table>
<thead>
<tr>
<th>eGFR, ml/min per 1.73 m²</th>
<th>FDA Recommendations for Metformin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;45</td>
<td>No contraindications</td>
</tr>
<tr>
<td>30–45</td>
<td>Obtain eGFR at least annually</td>
</tr>
<tr>
<td>30–45</td>
<td>Starting metformin is not recommended</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Assess the benefits and risks of continuing treatment for patients currently receiving metformin</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Metformin should be discontinued in patients with</td>
<td>History of liver disease, alcoholism, or heart failure</td>
</tr>
<tr>
<td></td>
<td>Upcoming iodinated contrast imaging procedure and eGFR between 30 and 60 ml/min per 1.73 m² (may restart 48 h after procedure if kidney function stabilizes)</td>
</tr>
<tr>
<td></td>
<td>Upcoming administration of intra-arterial iodinated contrast (may restart 48 h after procedure if kidney function stabilizes)</td>
</tr>
</tbody>
</table>

Obtain an eGFR before initiating metformin therapy.
endogenous glucagon-like peptide-1, thus enhancing insulin secretion, inhibiting inappropriate glucagon secretion from pancreatic α-cells, delaying gastric emptying, and inducing satiety. The use of GLP-1 RAs, in general, has increased in recent years due to benefits of better glycemic control, low risk of hypoglycemia, and weight loss. Of importance in the setting of CKD, GLP-1 RA use has been associated with post-marketing reports of decreased kidney function, but such events have not been uniformly observed in clinical trials or population-based observational studies. The majority of case reports of altered kidney function with exenatide have involved at least one contributory factor, such as congestive heart failure, pancreatitis, infection, volume depletion, and/or the use of concomitant medications, such as diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, and nonsteroidal anti-inflammatory drugs. Additionally, patients who experience gastrointestinal adverse events (i.e., nausea, vomiting, and diarrhea) associated with GLP-1 RA treatment seem to be at greatest risk.

Two agents within the GLP-1 RA class of medications, lixisenatide and dulaglutide, currently have CVOT data available as summarized in Table 5. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) Trial showed that the addition of lixisenatide to usual care did not significantly alter the rate of major CV events or other serious adverse events. The primary composite end point of CV-related death, myocardial infarction, stroke, or hospitalization for unstable angina occurred in 13.4% of the lixisenatide group compared with 13.2% of those receiving placebo (HR, 1.02; 95% CI, 0.89 to 1.17; P<0.001). In contrast, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) Study, fewer patients experienced the primary composite CV outcome in the liraglutide group when compared with those receiving placebo (HR, 0.87; 95% CI, 0.78 to 0.97; P=0.01 for superiority). Why the ELIXA Trial and the LEADER Study showed different outcomes in terms of the primary composite CV outcome is unknown. Pending CVOTs from other agents in the GLP-1 RA class should shed additional light on these differences.

Studies in patients with DKD have additionally shown that lixisenatide lowered albuminuria levels in patients with normal kidney function or early-stage CKD and that liraglutide treatment did not adversely affect eGFR and showed improved glycemic control in patients with T2DM and CKD stage 3. Recently released data from the LEADER Study as well as clinical trials of semaglutide and dulaglutide consistently show reduced risk of albuminuria onset and progression. The consistency of these data across GLP-1 RA class strongly suggests a class effect toward protection against DKD. The mechanisms of action may be multifactorial from lower levels of glycemia and body weight to direct effects on the kidney.

### Table 4. Summary of CVOT data for DPP-4 inhibitors currently marketed in the United States

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name (clinicaltrials.gov Identifier)</th>
<th>Summary of Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin&lt;sup&gt;61,62&lt;/sup&gt;</td>
<td>TECOS (NCT00790205)</td>
<td>Sitagliptin was noninferior to placebo for the primary composite CV outcome (HR, 0.98; 95% CI, 0.88 to 1.09; P&lt;0.001)</td>
</tr>
<tr>
<td>Long-acting saxagliptin&lt;sup&gt;63,64&lt;/sup&gt;</td>
<td>SAVOR-TIMI 53 Trial (NCT01107886)</td>
<td>Saxagliptin was noninferior to placebo for the primary composite CV outcome (HR, 1.00; 95% CI, 0.83 to 1.20; P=0.98)</td>
</tr>
<tr>
<td>Saxagliptin&lt;sup&gt;63,64&lt;/sup&gt;</td>
<td></td>
<td>Four-point major adverse CV event rates increase with lower baseline eGFR (3.52, 3.55, 5.74, and 7.34 events per patient-year for stages 1–3b, respectively)</td>
</tr>
<tr>
<td>Alogliptin&lt;sup&gt;65,66&lt;/sup&gt;</td>
<td>EXAMINE (NCT00968708)</td>
<td>Alogliptin was noninferior to placebo for the primary composite CV outcome (HR, 0.96; upper boundary of the one-sided 95% CI, 1.16; P&lt;0.001)</td>
</tr>
<tr>
<td>Linagliptin&lt;sup&gt;67&lt;/sup&gt;</td>
<td>CARMELINA (NCT01897532)</td>
<td>Treatment with saxagliptin improved ACR, even in the normoalbuminuric range, without affecting eGFR</td>
</tr>
</tbody>
</table>

ACR, albumin-to-creatinine ratio; EXAMINE, Examination of Cardiovascular Outcomes; Alogliptin vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus.
Additional data-pending trials involving GLP-1 RA in the setting of DKD include the Effect of LIXIisenatide on the Renal System (ELIXIRS) Study and the Assessment of Weekly Administration of Dulaglutide in Diabetes-7 (AWARD-7) Study. The ELIXIRS Study will explore the effects of lixisenatide treatment on kidney function and biomarkers in participants with T2DM. The AWARD-7 Study will soon report findings related to the efficacy and safety of dulaglutide for glycemic management as well as DKD progression in patients with T2DM and CKD stages 3 and 4. Importantly, the AWARD-7 Study also has a nested validation study of HbA1C that will inform modification and use of this glycemic biomarker in patients with low eGFR.

**SGLT-2 Inhibitors**

SGLT-2 is overexpressed in hyperglycemic conditions and paradoxically, increases proximal tubular maximum capacity for glucose reabsorption. By blocking SGLT-2, this class of medication reduces glucose and sodium reabsorption, resulting in decreased glomerular hyperfiltration and lessening of glomerular hypertension by reducing tubuloglomerular feedback (Figures 1 and 2).

### Table 5. Summary of CVOT data for GLP-1 RAs currently marketed in the United States

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name (clinicaltrials.gov Identifier)</th>
<th>Summary of Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>LEADER Study (NCT01179048)</td>
<td>The primary composite CV outcome occurred in significantly fewer patients in the liraglutide group (13.0%) than the placebo group (14.9%; HR, 0.87; 95% CI, 0.78 to 0.97; P&lt;0.01 for superiority) Fewer patients died from CV causes in the liraglutide group (4.7%) than the placebo group (6.0%; HR, 0.78; 95% CI, 0.66 to 0.93; P&lt;0.01) Death from any cause was lower in the liraglutide group (8.2%) than the placebo group (9.6%; HR, 0.85; 95% CI, 0.74 to 0.97; P=0.02)</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>ELIXA Trial (NCT01147250)</td>
<td>Lixisenatide was noninferior to placebo for the primary composite CV outcome (HR, 1.02; 95% CI, 0.89 to 1.17; P&lt;0.001) No significant between-group differences in the rate of hospitalization for heart failure (HR, 0.96; 95% CI, 0.75 to 1.23)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>EXSCEL (NCT01144338)</td>
<td>Trial in progress; estimated completion in April of 2018</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>REWIND (NCT01394952)</td>
<td>Trial in progress; estimated completion in July of 2018</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>HARMONY Outcomes (NCT02465515)</td>
<td>Trial in progress; estimated completion in May of 2019</td>
</tr>
</tbody>
</table>

EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; HARMONY Outcomes, A Long Term, Randomised, Double Blind, Placebo-controlled Study to Determine the Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus.

### Table 6. Summary of CVOT data for SGLT-2 inhibitors currently marketed in the United States

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name (clinicaltrials.gov Identifier)</th>
<th>Summary of Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG Outcome Trial (NCT01131676)</td>
<td>The primary composite CV outcome occurred in significantly fewer patients in the empagliflozin group (10.5%) than the placebo group (12.1%; HR, 0.86; 95% CI, 0.74 to 0.99; P=0.04 for superiority) The empagliflozin group had significantly lower rates of death from CV causes (3.7% versus 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) Doubling of Scr occurred in 1.5% of the empagliflozin group and 2.6% of the placebo group (44% relative risk reduction) Progression to macroalbuminuria occurred in 11.2% of the empagliflozin group and 16.2% of the placebo group (38% relative risk reduction) RRT was initiated in 0.3% of the empagliflozin group and 0.6% of the placebo group (55% relative risk reduction)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS (NCT01032629)</td>
<td>Trial completed in February 2017; results pending</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DECLARE-TIMI-58 (NCT01730534)</td>
<td>Trial in progress; estimated completion in April of 2019</td>
</tr>
</tbody>
</table>

Scr, serum creatinine; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI-58, Dapagliflozin Effect on Cardiovascular Events.
approximately $-0.40\%$ in patients with eGFR=30–60 ml/min per 1.73 m$^2$ in studies involving canagliflozin and empagliflozin.$^{93,94}$ The BP-lowering effect of SGLT2 inhibition seems to be a class effect and has been reported for empagliflozin, dapagliflozin, and canagliflozin. Likewise, clinical trial data are available for each of the currently available SGLT-2 inhibitors showing a reduction in albuminuria with treatment.$^{94–97}$

The Empagliflozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Clinical Trial recently showed that empagliflozin significantly lowered rates of death from CV causes (4% versus 6%; 38% relative risk reduction), hospitalization for heart failure (3% versus 4%; 35% relative risk reduction), and death from any cause (6% versus 8%; 32% relative risk reduction) in patients with T2DM and CV already receiving standard of care (risk reduction) in patients with T2DM and CV already receiving standard of care.$^{98}$ Post hoc analyses of the same trial showed beneficial effects on the kidney, including reduction of albuminuria, slowing of eGFR decline, and a 50% reduction in risk of progressing to ESRD.$^{99}$ CVOT data for canagliflozin and dapagliflozin are currently pending as shown in Table 6.$^{98–101}$ An additional study, the Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) Trial, is underway to assess whether treatment with canagliflozin can reduce DKD progression. The CREDENCE Trial is anticipated to be completed in approximately the year 2019.$^{102}$

Glycemic management in patients with DM and CKD is complicated by many factors, including imprecision of HbA1C measurement and altered pharmacokinetics of antihyperglycemic agents. Appropriate glycemic goal setting and use of SMBG are critical to meet individualized glycemic goals and avoid hypoglycemic events in this at-risk population. A growing body of literature is providing insight into the CV and kidney safety of antihyperglycemic agents with the DPP-4 inhibitor, GLP-1 RA, and SGLT-2 inhibitor classes of medications. Additional ongoing trials examining the use of these agents in the CKD population will further inform the use of antihyperglycemic medications in patients with DM and kidney disease.

**DISCLOSURES**

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Antihyperglycemic Agents in Diabetic Kidney Disease


