8-1-2017

Therapeutic Considerations for Antihyperglycemic Agents in Diabetic Kidney Disease.

Joshua J Neumiller

Radica Alicic
Providence Medical Research Center, Providence Health Care, Spokane, Washington

Katherine Tuttle
Providence Medical Research Center, Providence Health Care, Spokane, Washington

JASN

J Am Soc Nephrol. 2017 Aug; 28(8): 2263–2274.
Published online 2017 May 2.
doi: 10.1681/ASN.2016121372: 10.1681/ASN.2016121372

PMCID: PMC5533243
PMID: 28465376

Therapeutic Considerations for Antihyperglycemic Agents in Diabetic Kidney Disease

Joshua J. Neumiller,[*] Radica Z. Alicic,[†‡] and Katherine R. Tuttle[†‡§‖]

[*]Department of Pharmacotherapy, Washington State University College of Pharmacy, Spokane, Washington;
[†]Providence Medical Research Center, Providence Health Care, Spokane, Washington;
[‡]Department of Medicine, University of Washington School of Medicine, Seattle, Washington; and
[§]Nephrology Division, Kidney Research Institute and
[‖]Institute of Translational Health Sciences, University of Washington, Seattle, Washington
[*]Corresponding author.
Correspondence: Dr. Joshua J. Neumiller, Department of Pharmacotherapy, College of Pharmacy, Washington State University, PO Box 1495, Spokane, WA 99210-1495., Email: jneumiller@wsu.edu

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.

Keywords: diabetes mellitus, renal protection, diabetes

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 hypoglycemia, 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.

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 repletion 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).[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[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).[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.[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).[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^2) when compared with those without CKD.[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.[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).[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.[17] Another contributor to the increased risk of hypoglycemia in people with DKD is altered metabolism and elimination of glucose-lowering medications.[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 antihyperglycemic agents results in prolonged exposure to higher drug levels, requiring dose de-escalation for many agents.[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.[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).[21,22] Factors associated with increased red blood cell turnover (*e.g.*, shortened red blood cell lifespan, decreased erythropoiesis, blood transfusions, and treatment with iron or erythrocyte-stimulating agents [ESAs]) also lowers the HbA1C relative to ambient blood glucose.[22–24] Indeed, use of ESAs was identified as a key risk factor for low HbA1C in a study involving patients with diabetes and CKD (stages 3–5), and the discordant relationship

between glucose and HbA1C values is likely most relevant in those receiving ESA therapy.[23] In the past, formation of carbamylated hemoglobin in advanced kidney failure was reported to falsely increase HbA1C values.[22,26] 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.[22] 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.[27] Self-monitoring of blood glucose (SMBG) provides crucial information about glycemic control and daily fluctuations.[28] Continuous glucose monitoring holds promise for daily glycemic assessment but remains to be validated in patients with CKD.[29] At this time, HbA1C results should be interpreted carefully in conjunction with SMBG to achieve glycemic goals and mitigate hypoglycemic risk.

Guideline-recommended HbA1C goals for patients with DM and CKD have been informed by a series by results 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 microvascular complications, including DKD.[8,30–32] However, studies enrolling patients with long-term T2DM and a high burden of comorbidity showed greater risks of hypoglycemia and no benefit on all-cause or CV mortality with intensive glycemic control compared with standard therapy (achieved HbA1C of 6%–6.5% versus 7.3%–8.4%, respectively).[18,33–35] In a subset with CKD, these risks were greatly amplified.[18] The American Diabetes Association currently recommends a less stringent target HbA1C, such as <8.0%, for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and comorbid conditions, such as CKD.[36] Table 1 provides a summary of glycemic target recommendations from several recent guidelines and consensus papers.[19,33,36]

Antihyperglycemic 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]

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 be initiated at a low dose and titrated conservatively if used (refer to Table 2).[47] 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.[48] Accordingly, dose adjustments in patients with CKD are not necessary with glipizide, making it the sulfonylurea of choice in this population.[19]

Similarly, the main concern with meglitinide use in the setting of CKD is increased risk of hypoglycemia due to decreased renal clearance of the parent drugs and metabolites.[19] Lower doses of meglitinides are required in CKD, with initial conservative dosing (Table 2).

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 0.5% 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; $P<0.001$).[61] 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 showed noninferiority for saxagliptin when compared with placebo on the primary composite outcome (HR, 1.00; 95% CI, 0.89 to 1.12; $P<0.001$).[63] 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; $P=0.01$).[63] 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 endogenous glucagon-like peptide-1, thus enhancing insulin secretion, inhibiting inappropriate glucagon secretion from pancreatic α-cells, delaying gastric emptying, and inducing satiety.[72] 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.[72] Of importance in the setting of CKD, GLP-1 RA use has been associated with postmarketing reports of decreased kidney function, but such events have not been uniformly observed in clinical trials or population-based observational studies.[73–75] 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.[76] 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, liraglutide and lixisenatide, currently have CVOT data available as summarized in Table 5.[77–81] 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.[78] 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; $P<0.001$ for noninferiority). 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).[77] 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 liraglutide lowered albuminuria levels in patients with normal kidney function or early-stage CKD[82] and that liraglutide treatment did not adversely affect eGFR and showed improved glycemic control in patients with T2DM and CKD stage 3.[83] 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.[77,84,85] 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.

Additional data-pending trials involving GLP-1 RA in the setting of DKD include the Effect of LIXIsenatide on the Renal System (ELIXIRS) Study and the Assessment of Weekly Administration of Dulaglutide in Diabetes-7 (AWARD-7) Study.[86,87] 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.[13,14] 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).[88,89] At present, clinically available SGLT-2 inhibitors in the United States are canaglifozin, dapaglifozin, and empaglifozin. Several additional agents are in clinical development and/or available commercially outside of the United States. Placebo-controlled studies have shown adjusted mean treatment differences in HbA1C of approximately −0.5%–0.7% with SGLT-2 inhibitor use.[90–92] Among the patients with DKD, this effect on HbA1C was attenuated and dropped to approximately −0.40% in patients with eGFR=30–60 ml/min per 1.73 m^2 in studies involving canaglifozin and empaglifozin.[93,94] The BP-

lowering effect of SGLT2 inhibition seems to be a class effect and has been reported for empaglifozin, dapaglifozin, and canaglifozin. 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 Empaglifozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Clinical Trial recently showed that empaglifozin 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 for treatment of BP and lipids.[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

J.J.N. has received consulting fees from Eli Lilly and Company, Indianapolis, IN, Sanofi, Paris, France, Novo Nordisk, Plainsboro, New Jersey, and Boehringer Ingelheim, Ridgefield, CT. R.Z.A. has no relevant conflicts to report. K.R.T. has received consulting fees from Eli Lilly and Company, Indianapolis, IN, Amgen, Thousand Oaks, CA, Noxxon Pharma, Berlin, Germany, and Boehringer Ingelheim, Ridgefield, CT.

Footnotes

Published online ahead of print. Publication date available at www.jasn.org.

References

1. Silink ZM: United Nations resolution on diabetes. Pract Diabetes Int 23: 279, 2006

2. International Diabetes Federation: IDF Diabetes Atlas, 7th Ed., 2015. Available at: http://www.diabetesatlas.org/resources/2015-atlas.html. Accessed March 28, 2017

3. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE.: Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 103: 137–149, 2014 [PubMed: 24630390]

4. Menke A, Casagrande S, Geiss L, Cowie CC.: Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 314: 1021–1029, 2015 [PubMed: 26348752]

5. United States Renal Data System : 2015 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2015

6. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL; Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD) : ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - Summary. Diab Vasc Dis Res 11: 133–173, 2014 [PubMed: 24800783]

7. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH.: Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 24: 302–308, 2013 [PMCID: PMC3559486] [PubMed: 23362314]

8. de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, Steffes MW, Zinman B; DCCT/EDIC Research Group .: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 365: 2366–2376, 2011 [PMCID: PMC3270008] [PubMed: 22077236]

9. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR; UKPDS Study Group .: Risk factors for renal dysfunction in type 2 diabetes: U.K. prospective diabetes study 74. Diabetes 55: 1832–1839, 2006 [PubMed: 16731850]

10. Dreisbach AW, Lertora JJ.: The effect of chronic renal failure on drug metabolism and transport. Expert Opin Drug Metab Toxicol 4: 1065–1074, 2008 [PMCID: PMC2745294] [PubMed: 18680441]

11. Gerich JE: Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: Therapeutic implications. Diabet Med 27: 136–142, 2010 [PMCID: PMC4232006] [PubMed: 20546255]

12. Wilding JP: The role of the kidneys in glucose homeostasis in type 2 diabetes: Clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. Metabolism 63: 1228–1237, 2014 [PubMed: 25104103]

13. Neumiller JJ, White JR Jr., Campbell RK.: Sodium-glucose co-transport inhibitors: Progress and therapeutic potential in type 2 diabetes mellitus. Drugs 70: 377–385, 2010 [PubMed: 20205482]

14. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J.: Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 54: 3427–3434, 2005 [PubMed: 16306358]

15. Vestri S, Okamoto MM, de Freitas HS, Aparecida Dos Santos R, Nunes MT, Morimatsu M, Heimann JC, Machado UF.: Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. J Membr Biol 182: 105–112, 2001 [PubMed: 11447502]

16. Tuttle KR: Back to the future: Glomerular hyperfiltration in the diabetic kidney. Diabetes 66: 14–16, 2017 [PMCID: PMC5204314] [PubMed: 27999101]

17. Moen MF, Zhan M, Hsu VD, Walker LD, Einhorn LM, Seliger SL, Fink JC.: Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 4: 1121–1127, 2009 [PMCID: PMC2689888] [PubMed: 19423569]

18. Papademetriou V, Lovato L, Doumas M, Nylen E, Mottl A, Cohen RM, Applegate WB, Puntakee Z, Yale JF, Cushman WC; ACCORD Study Group .: Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int 87: 649–659, 2015 [PubMed: 25229335]

19. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE, Whaley-Connell AT, Molitch ME.: Diabetic kidney disease: A report from an ADA Consensus Conference. Diabetes Care 37: 2864–2883, 2014 [PMCID: PMC4170131] [PubMed: 25249672]

20. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group .: Translating the A1C assay into estimated average glucose values. Diabetes Care 31: 1473–1478, 2008 [PMCID: PMC2742903] [PubMed: 18540046]

21. Agarwal R, Light RP.: Relationship between glycosylated hemoglobin and blood glucose during progression of chronic kidney disease. Am J Nephrol 34: 32–41, 2011 [PubMed: 21659737]

22. Speeckaert M, Van Biesen W, Delanghe J, Slingerland R, Wiecek A, Heaf J, Drechsler C, Lacatus R, Vanholder R, Nistor I; European Renal Best Practice Guideline Development Group on Diabetes in Advanced CKD .: Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? Nephrol Dial Transplant 29: 2167–2177, 2014 [PubMed: 24470517]

23. Chen HS, Wu TE, Lin HD, Jap TS, Hsiao LC, Lee SH, Lin SH.: Hemoglobin A(1c) and fructosamine for assessing glycemic control in diabetic patients with CKD stages 3 and 4. Am J Kidney Dis 55: 867–874, 2010 [PubMed: 20202728]

24. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, Okamura M, Okada S, Yamakawa T, Ishimura E, Nishizawa Y; Osaka CKD Expert Research Group .: Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: Effect of anemia and erythropoietin injection. J Am Soc Nephrol 18: 896–903, 2007 [PubMed: 17267743]

25. Lo C, Lui M, Ranasinha S, Teede HJ, Kerr PG, Polkinghorne KR, Nathan DM, Zheng H, Zoungas S.: Defining the relationship between average glucose and HbA1c in patients with type 2 diabetes and chronic kidney disease. Diabetes Res Clin Pract 104: 84–91, 2014 [PubMed: 24573088]

26. Pecoits-Filho R, Abensur H, Betônico CC, Machado AD, Parente EB, Queiroz M, Salles JE, Titan S, Vencio S.: Interactions between kidney disease and diabetes: Dangerous liaisons. Diabetol Metab Syndr 8: 50, 2016 [PMCID: PMC4964290] [PubMed: 27471550]

27. Kalantar-Zadeh K: A critical evaluation of glycated protein parameters in advanced nephropathy: A matter of life or death: A1C remains the gold standard outcome predictor in diabetic dialysis patients. Counterpoint. Diabetes Care 35: 1625–1628, 2012 [PMCID: PMC3379587] [PubMed: 22723587]

28. Mirani M, Berra C, Finazzi S, Calvetta A, Radaelli MG, Favareto F, Graziani G, Badalamenti S.: Inter-day glycemic variability assessed by continuous glucose monitoring in insulin-treated type 2 diabetes patients on hemodialysis. Diabetes Technol Ther 12: 749–753, 2010 [PubMed: 20809678]

29. Riveline JP, Teynie J, Belmouaz S, Franc S, Dardari D, Bauwens M, Caudwell V, Ragot S, Bridoux F, Charpentier G, Marechaud R, Hadjadj S.: Glycaemic control in type 2 diabetic patients on chronic haemodialysis: Use of a continuous glucose monitoring system. Nephrol Dial Transplant 24: 2866–2871, 2009 [PubMed: 19389864]

30. Anonymous: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. Kidney Int 47: 1703–1720, 1995 [PubMed: 7643540]

31. Anonymous: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 837–853, 1998 [PubMed: 9742976]

32. Nathan DM; DCCT/EDIC Research Group .: The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. Diabetes Care 37: 9–16, 2014 [PMCID: PMC3867999] [PubMed: 24356592]

33. National Kidney Foundation : KDOQI clinical practice guideline for diabetes and CKD: 2012 Update. Am J Kidney Dis 60: 850–886, 2012 [PubMed: 23067652]

34. Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr., Probstfield JL, Simons-Morton DG, Friedewald WT; Action to Control Cardiovascular Risk in Diabetes Study Group .: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545–2559, 2008 [PMCID: PMC4551392] [PubMed: 18539917]

35. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F; ADVANCE Collaborative Group .: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560–2572, 2008 [PubMed: 18539916]

36. American Diabetes Association : Standards of Medical Care in Diabetes – 2017. Diabetes Care 40[Suppl 1]: S1–S135, 2017

37. US Food and Drug Administration: FDA Drug Safety Communication: FDA Revises Warnings Regarding Use of the Diabetes Medicine Metformin in Certain Patients with Reduced Kidney Function, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed March 28, 2017

38. Sanofi-Aventis US LLC: Adlyxin (Lixisenatide) [Prescribing Information], Bridgewater, NJ, Sanofi-Aventis US LLC, 2016

39. Roberts F, Ryan GJ.: The safety of metformin in heart failure. Ann Pharmacother 41: 642–646, 2007 [PubMed: 17374622]

40. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK.: Metformin in patients with type 2 diabetes and kidney disease: A systematic review. JAMA 312: 2668–2675, 2014 [PMCID: PMC4427053] [PubMed: 25536258]

41. Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, Wang X, Tang S, Nagi A, Kosinski AS, Williams JW Jr..: Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: A systematic review. Ann Intern Med 166: 191–200, 2017 [PMCID: PMC5293600] [PubMed: 28055049]

42. Snyder RW, Berns JS.: Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial 17: 365–370, 2004 [PubMed: 15461745]

43. Rabkin R, Ryan MP, Duckworth WC.: The renal metabolism of insulin. Diabetologia 27: 351–357, 1984 [PubMed: 6389240]

44. Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G.: Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. Diabet Med 20: 642–645, 2003 [PubMed: 12873291]

45. Mak RH: Impact of end-stage renal disease and dialysis on glycemic control. Semin Dial 13: 4–8, 2000 [PubMed: 10740665]

46. Rydberg T, Jönsson A, Røder M, Melander A.: Hypoglycemic activity of glyburide (glibenclamide) metabolites in humans. Diabetes Care 17: 1026–1030, 1994 [PubMed: 7988301]

47. Holstein A, Plaschke A, Egberts EH.: Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev 17: 467–473, 2001 [PubMed: 11757083]

48. Harrower AD: Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. Clin Pharmacokinet 31: 111–119, 1996 [PubMed: 8853933]

49. Budde K, Neumayer HH, Fritsche L, Sulowicz W, Stompôr T, Eckland D.: The pharmacokinetics of pioglitazone in patients with impaired renal function. Br J Clin Pharmacol 55: 368–374, 2003 [PMCID: PMC1884238] [PubMed: 12680885]

50. Chapelsky MC, Thompson-Culkin K, Miller AK, Sack M, Blum R, Freed MI.: Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. J Clin Pharmacol 43: 252–259, 2003 [PubMed: 12638393]

51. Thompson-Culkin K, Zussman B, Miller AK, Freed MI.: Pharmacokinetics of rosiglitazone in patients with end-stage renal disease. J Int Med Res 30: 391–399, 2002 [PubMed: 12235921]

52. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL, IOF Bone and Diabetes Working Group .: Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol 13: 208–219, 2017 [PubMed: 27658727]

53. US Food & Drug Administration: Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, 2008. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed March 28, 2017

54. Giorda CB, Nada E, Tartaglino B.: Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature. Endocrine 46: 406–419, 2014 [PubMed: 24510630]

55. Friedrich C, Emser A, Woerle HJ, Graefe-Mody U.: Renal impairment has no clinically relevant effect on the long-term exposure of linagliptin in patients with type 2 diabetes. Am J Ther 20: 618–621, 2013 [PubMed: 23411609]

56. Cheng D, Fei Y, Liu Y, Li J, Chen Y, Wang X, Wang N.: Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes mellitus patients with moderate to severe renal impairment: A systematic review and meta-analysis. PLoS One 9: e111543, 2014 [PMCID: PMC4216116] [PubMed: 25360775]

57. Mori H, Okada Y, Arao T, Tanaka Y.: Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. J Diabetes Investig 5: 313–319, 2014 [PMCID: PMC4020336] [PubMed: 24843780]

58. Udell JA, Bhatt DL, Braunwald E, Cavender MA, Mosenzon O, Steg PG, Davidson JA, Nicolau JC, Corbalan R, Hirshberg B, Frederich R, Im K, Umez-Eronini AA, He P, McGuire DK, Leiter LA, Raz I, Scirica BM; SAVOR-TIMI 53 Steering Committee and Investigators .: Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: Observations from the SAVOR-TIMI 53 Trial. Diabetes Care 38: 696–705, 2015 [PubMed: 25552421]

59. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M.: Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care 36: 3460–3468, 2013 [PMCID: PMC3816860] [PubMed: 24026560]

60. Sakata K, Hayakawa M, Yano Y, Tamaki N, Yokota N, Eto T, Watanabe R, Hirayama N, Matsuo T, Kuroki K, Sagara S, Mishima O, Koga M, Nagata N, Nishino Y, Kitamura K, Kario K, Takeuchi M, Yamagishi S.: Efficacy of alogliptin, a dipeptidyl peptidase-4 inhibitor, on glucose parameters, the activity of the advanced glycation end product (AGE) - receptor for AGE (RAGE) axis and albuminuria in Japanese type 2 diabetes. Diabetes Metab Res Rev 29: 624–630, 2013 [PubMed: 23861159]

61. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group .: Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 373: 232–242, 2015 [PubMed: 26052984]

62. Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, Engel SS, Lopes RD, McGuire DK, Riefflin A, Rodbard HW, Sinay I, Tankova T, Wainstein J, Peterson ED, Holman RR; TECOS Study Group .: Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: Outcomes from TECOS. Diabetes Care 39: 2304–2310, 2016 [PubMed: 27742728]

63. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators .: Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369: 1317–1326, 2013 [PubMed: 23992601]

64. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Wei C, Im K, Rozenberg A, Yanuv I, Stahre C, Ray KK, Igbal N, Braunwald E, Scirica BM, Raz I.: Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care 40: 69–76, 2017 [PubMed: 27797925]

65. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators .: Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 369: 1327–1335, 2013 [PubMed: 23992602]

66. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators .: Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: A multicentre, randomised, double-blind trial. Lancet 385: 2067–2076, 2015 [PubMed: 25765696]

67. ClinicalTrials.gov: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). NCT01897532. Available at: https://clinicaltrials.gov/ct2/show/NCT01897532. Accessed March 28, 2017

68. Monami M, Dicembrini I, Mannucci E.: Dipeptidyl peptidase-4 inhibitors and heart failure: A meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 24: 689–697, 2014 [PubMed: 24793580]

69. Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, Hu N, Paterson JM, Targownik L, Turin TC, Udell JA, Ernst P; CNODES Investigators .: A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 374: 1145–1154, 2016 [PubMed: 27007958]

70. ClinicalTrials.gov: MARLINA – T2D: Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAgliptin. NCT01792518. Available at: https://clinicaltrials.gov/ct2/show/NCT01792518. Accessed March 28, 2017

71. ClinicalTrials.gov: Renal Effects of DPP-4 Inhibitor Linagliptin in Type 2 Diabetes (RENALIS). NCT02106104. Available at: https://clinicaltrials.gov/ct2/show/NCT02106104. Accessed March 28, 2017

72. Neumiller JJ: Incretin pharmacology: A review of the incretin effect and current incretin-based therapies. Cardiovasc Hematol Agents Med Chem 10: 276–288, 2012 [PubMed: 22827291]

73. Tuttle KR, Heilmann C, Hoogwerf BJ, Brown C, Anderson PW.: Effects of exenatide on kidney function, adverse events, and clinical end points of kidney disease in type 2 diabetes. Am J Kidney Dis 62: 396–398, 2013 [PubMed: 23684754]

74. Pawaskar M, Tuttle KR, Li Q, Best JH, Anderson PW.: Observational study of kidney function and albuminuria in patients with type 2 diabetes treated with exenatide BID versus insulin glargine. Ann Pharmacother 48: 571–576, 2014 [PubMed: 24497624]

75. Davidson JA, Brett J, Falahati A, Scott D.: Mild renal impairment and the efficacy and safety of liraglutide. Endocr Pract 17: 345–355, 2011 [PubMed: 21700561]

76. US Food and Drug Administration: Byetta (Exenatide) – Renal Failure, 2009. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm. Accessed March 28, 2017

77. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee, LEADER Trial Investigators .: Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375: 311–322, 2016 [PMCID: PMC4985288] [PubMed: 27295427]

78. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators .: Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 373: 2247–2257, 2015 [PubMed: 26630143]

79. ClinicalTrials.gov: Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus. NCT01144338. Available at: https://clinicaltrials.gov/ct2/show/NCT01144338. Accessed March 28, 2017

80. ClinicalTrials.gov: Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND). NCT01394952. Available at: https://clinicaltrials.gov/ct2/show/NCT01394952. Accessed March 28, 2017

81. ClinicalTrials.gov: Effect of Albiglutide, when Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects with Type 2 Diabetes Mellitus. NCT02465515. Available at: https://clinicaltrials.gov/ct2/show/NCT02465515. Accessed March 28, 2017

82. Zavattaro M, Caputo M, Samà MT, Mele C, Chasseur L, Marzullo P, Pagano L, Mauri MG, Ponziani MC, Aimaretti G, Prodam F.: One-year treatment with liraglutide improved renal function in patients with type 2 diabetes: A pilot prospective study. Endocrine 50: 620–626, 2015 [PubMed: 25572181]

83. Davies MJ, Bain SC, Atkin SL, Rossing P, Scott D, Shamkhalova MS, Bosch-Traberg H, Syrén A, Umpierrez GE.: Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): A randomized clinical trial. Diabetes Care 39: 222–230, 2016 [PubMed: 26681713]

84. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators .: Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375: 1834–1844, 2016 [PubMed: 27633186]

85. Tuttle KR, McKinney TD, Davidson JA, Anglin G, Harper KD, Botros FT.: Effects of once-weekly dulaglutide on kidney function in patients with type 2 diabetes in phase II and III clinical trials. Diabetes Obes Metab 19: 436–441, 2017 [PMCID: PMC5347883] [PubMed: 27766728]

86. ClinicalTrials.gov: Effect of LIXIsenatide on the Renal System (ELIXIRS). NCT02276196. Available at: https://clinicaltrials.gov/ct2/show/NCT02276196. Accessed March 28, 2017

87. ClinicalTrials.gov: A Study Comparing Dulaglutide with Insulin Glargine on Glycemic Control in Participants with Type 2 Diabetes (T2D) and Moderate or Severe Chronic Kidney Disease (CKD) (AWARD-7). NCT01621178. Available at: https://clinicaltrials.gov/ct2/show/NCT01621178. Accessed March 28, 2017

88. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M.: Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129: 587–597, 2014 [PubMed: 24334175]

89. Vallon V, Thomson SC.: Targeting renal glucose reabsorption to treat hyperglycaemia: The pleiotropic effects of SGLT2 inhibition. Diabetologia 60: 215–225, 2017 [PMCID: PMC5884445] [PubMed: 27878313]

90. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G.: Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 15: 372–382, 2013 [PMCID: PMC3593184] [PubMed: 23279307]

91. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF.: Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 33: 2217–2224, 2010 [PMCID: PMC2945163] [PubMed: 20566676]

92. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, Woerle HJ.: Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab 15: 1154–1160, 2013 [PubMed: 23906374]

93. Yale JF, Bakris G, Cariou B, Nieto J, David-Neto E, Yue D, Wajs E, Figueroa K, Jiang J, Law G, Usiskin K, Meininger G; DIA3004 Study Group .: Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 16: 1016–1027, 2014 [PubMed: 24965700]

94. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, Broedl UC.: EMPA-REG RENAL trial investigators: Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomized, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2: 369–384, 2014 [PubMed: 24795251]

95. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, Desai M, Shaw W, Capuano G, Alba M, Jiang J, Vercruysse F, Meininger G, Matthews D; CANVAS Trial Collaborative Group .: Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 38: 403–411, 2015 [PubMed: 25468945]

96. Kohan DE, Fioretto P, Tang W, List JF.: Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 85: 962–971, 2014 [PMCID: PMC3973038] [PubMed: 24067431]

97. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G.: Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 15: 463–473, 2013 [PMCID: PMC3654568] [PubMed: 23464594]

98. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators .: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373: 2117–2128, 2015 [PubMed: 26378978]

99. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators .: Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323–334, 2016 [PubMed: 27299675]

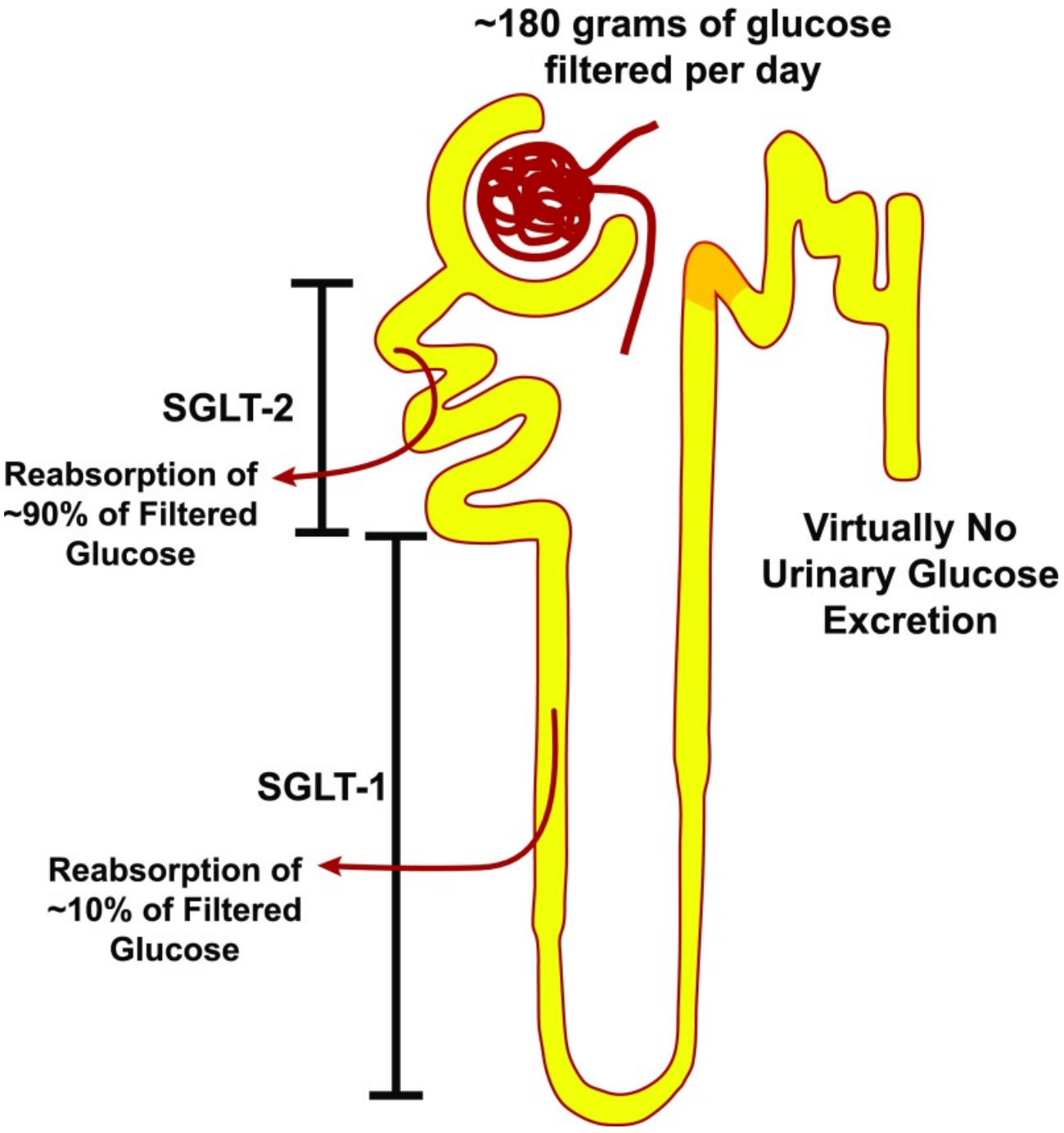
100. ClinicalTrials.gov: Canagliflozin Cardiovascular Assessment Study (CANVAS). NCT01032629. Available at: https://clinicaltrials.gov/ct2/show/NCT01032629. Accessed March 28, 2017

101. ClinicalTrials.gov: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). NCT01730534. Available at: https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed March 28, 2017

102. ClinicalTrials.gov: Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE). NCT02065791. Available at: https://clinicaltrials.gov/ct2/show/NCT02065791. Accessed March 28, 2017

Figures and Tables

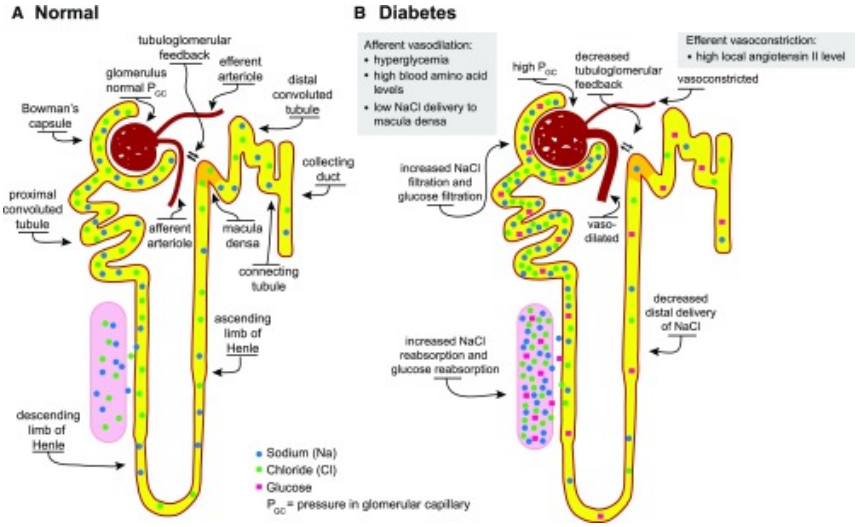
Figure 1.



Open in a separate window

SGLT-2 and SGLT-1 work together to reabsorb virtually all glucose filtered through the glomeruli under normal conditions.[12,13] Approximately 180 g of glucose are filtered by the glomeruli on a daily basis. Of this filtered glucose, essentially all of it is reabsorbed by SGLT-2 and SGLT-1, with SGLT-2 reabsorbing the majority of filtered glucose (approximately 90%).

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.

Table 1.

Select glycemic target recommendations for patients with DKD

Guideline/Consensus Report	Recommendations/Suggestions
ADA standards of medical care in diabetes 2017[36]	Less stringent HbA1C goals (such as <8%) may be appropriate for patients with advanced complications, including CKD
DKD: a report from an ADA consensus conference[19]	HbA1C<8% when GFR<60 ml/min per 1.73 m^2 due to increased hypoglycemia risk Reliance on SMBG in making treatment decisions due to imprecision of HbA1C
KDOQI clinical practice guideline for diabetes and CKD: 2012 update[33]	Recommend not treating to an HbA1C of <7.0% in patients at risk of hypoglycemia 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

ADA, American Diabetes Association; KDOQI, Kidney Disease Outcomes Quality Initiative.

Table 2.

Dosing recommendations for noninsulin antihyperglycemic agents currently available in the United States in the setting of CKD[19,37,38]

J Am Soc Nephrol
J Am Soc Nephrol

Medication	Recommended Dosing with Impaired GFR, ml/min per 1.73 m^2
Biguanides	
Metformin	No dose adjustment if eGFR>45
	Do not initiate or assess risk/benefit if currently on metformin if eGFR=30–45
	Discontinue if eGFR<30
Second generation sulfonylureas	
Glipizide	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily
Glyburide	Avoid use
Meglitinides	
Repaglinide	Initiate conservatively at 0.5 mg with meals if eGFR<30
Nateglinide	Initiate conservatively at 60 mg with meals if eGFR<30
Thiazolidinediones	
Pioglitazone	No dose adjustment required
Rosiglitazone	No dose adjustment required
α-Glucosidase inhibitors	
Acarbose	Avoid if eGFR<30
Miglitol	Avoid if eGFR<25
GLP-1 RAs	
Exenatide	Not recommended with eGFR<30
Liraglutide	No dose adjustment recommended by manufacturer
Lixisenatide	No dose adjustment required for eGFR=60–89
	No dose adjustment required for eGFR=30–59, but patients should be monitored for AEs and changes in kidney function
	Clinical experience is limited with eGFR=15–29; patients should be monitored for AEs and changes in kidney function
	Avoid if eGFR<15
Albiglutide	No dose adjustment required for eGFR=15–89 per manufacturer
Dulaglutide	No dose adjustment recommended by manufacturer
DPP-4 inhibitors	
Sitagliptin	100 mg daily if eGFR>50
	50 mg daily if eGFR=30–50
	25 mg daily if eGFR<30
Saxagliptin	5 mg daily if eGFR>50
	2.5 mg daily if eGFR≤50

AE, adverse event.

Table 3.

2016 Revised recommendations for metformin use in patients with impaired renal function[37]

eGFR, ml/min per 1.73 m^2	FDA Recommendations for Metformin Use
>45	No contraindications
	Obtain eGFR at least annually
30–45	Starting metformin is not recommended
	Assess the benefits and risks of continuing treatment for patients currently receiving metformin
<30	Contraindicated
Metformin should be discontinued in patients with	History of liver disease, alcoholism, or heart failure
	Upcoming iodinated contrast imaging procedure and eGFR between 30 and 60 ml/min per 1.73 m^2 (may restart 48 h after procedure if kidney function stabilizes)
	Upcoming administration of intra-arterial iodinated contrast (may restart 48 h after procedure if kidney function stabilizes)

Obtain an eGFR before initiating metformin therapy.

Table 4.

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

Agent	Trial Name (clinicaltrials.gov Identifier)	Summary of Key Findings
Sitagliptin[61,62]	TECOS (NCT00790205)	Sitagliptin was noninferior to placebo for the primary composite CV outcome (HR, 0.98; 95% CI, 0.88 to 1.09; $P<0.001$)
		Sitagliptin did not increase rates of hospitalization for heart failure compared with placebo (HR, 1.00; 95% CI, 0.83 to 1.20; $P=0.98$)
		Four-point major adverse CV event rates increase with lower baseline eGFR (3.52, 3.55, 5.74, and 7.34 events per patient-yr for stages 1–3b, respectively)
		Sitagliptin had no clinically significant effect on CV or CKD outcomes, irrespective of baseline eGFR
Saxagliptin[63,64]	SAVOR-TIMI 53 Trial (NCT01107886)	Saxagliptin was noninferior to placebo for the primary composite CV outcome (HR, 1.00; 95% CI, 0.89 to 1.12; $P<0.001$)
		More participants in the saxagliptin group were hospitalized for heart failure (HR, 1.27; 95% CI, 1.07 to 1.51; $P<0.01$)
		Saxagliptin treatment was associated with improvement and/or less deterioration in ACR categories from baseline to end of trial ($P=0.02$, $P<0.001$, and $P=0.05$ for individuals with baseline normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively)
		Treatment with saxagliptin improved ACR, even in the normoalbuminuric range, without affecting eGFR
Alogliptin[65,66]	EXAMINE (NCT00968708)	Alogliptin was noninferior to placebo for the primary composite CV outcome (HR, 0.96; upper boundary of the one-sided 95% CI, 1.16; $P<0.001$)
		Hospital admission for heart failure was the first event in 85 (3.1%) patients taking alogliptin compared with 79 (2.9%) taking placebo (HR, 1.07; 95% CI, 0.79 to 1.46)
Linagliptin[67]	CARMELINA (NCT01897532)	Trial in progress; estimated completion in January of 2018

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.

Table 5.

Summary of CVOT data for GLP-1 RAs currently marketed in the United States

Agent	Trial Name (clinicaltrials.gov Identifier)	Summary of Key Findings
Liraglutide[77]	LEADER Study (NCT01179048)	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*=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*<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)
Lixisenatide[78]	ELIXA Trial (NCT01147250)	Lixisenatide was noninferior to placebo for the primary composite CV outcome (HR, 1.02; 95% CI, 0.89 to 1.17; *P*<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)
Exenatide[79]	EXSCEL (NCT01144338)	Trial in progress; estimated completion in April of 2018
Dulaglutide[80]	REWIND (NCT01394952)	Trial in progress; estimated completion in July of 2018
Albiglutide[81]	HARMONY Outcomes (NCT02465515)	Trial in progress; estimated completion in May of 2019

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

Agent	Trial Name (clinicaltrials.gov Identifier)	Summary of Key Findings
Empagliflozin[98,99]	EMPA-REG Outcome Trial (NCT01131676)	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)
Canagliflozin[100]	CANVAS (NCT01032629)	Trial completed in February 2017; results pending
Dapagliflozin[101]	DECLARE-TIMI-58 (NCT01730534)	Trial in progress; estimated completion in April of 2019

SCr, serum creatinine; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI-58, Dapagliflozin Effect on Cardiovascular Events.