Use of Glucose-Lowering Medication in Patients with Chronic Kidney Diseases and Type 2 Diabetes

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Chapter 1. Introduction

1.1 Diabetes and chronic kidney disease epidemiology

An estimated 15% of US adults (≥18 years) (37 million people) have chronic kidney disease (CKD) (CDC, 2021). Diabetes is the leading cause of CKD. The prevalence of advanced stage CKD (stages 3 and 4) among US adults with diagnosed diabetes was 24.5% (27.1% to 22.1%), and among those without diabetes was 4.9% (6.1% to 4.1%) in 2011-2014 from National Health and Nutrition Examination Survey data (CDC, 2020).

1.2 Glucose-lowering medications

Patients with diabetes are at higher risk to develop end-stage kidney disease (ESKD) and cardiovascular disease, and consequently have increased risk of mortality. Hyperglycemia is among the major risk factors for the development and progression of disease in patients with diabetes. A meta-analysis of observational studies suggested that a 1% point increase in glycated hemoglobin (HbA1c) level was associated with an increase of 18% in the risk for cardiovascular disease in persons with type 2 diabetes (Selvin et al., 2004). An observational study with 23,296 participants showed that higher HbA1c levels in diabetes patients with CKD stages 3–5 (estimated glomerular filtration rate [eGFR] levels <60 mL/min/1.73 m^2) were strongly associated with worse outcomes: death, progression of kidney disease based on a doubling of serum creatinine level, or ESKD, cardiovascular events, and all-cause hospitalization (Shurraw et al., 2011).

In addition to lifestyle modifications and psychosocial care, diabetes treatment includes pharmacologic approaches for glycemic control. However, glucose-lowering medications can lead to hypoglycemia. And incidence of hypoglycemia is higher in intensive versus standard glycemic control groups (Wright et al., 2006; ACCORD, 2008; ADVANCE, 2008; Duckworth, 2009).

Kidneys play an important role in glucose hemostasis through kidney tubular glucose absorption and gluconeogenesis (Gerich, 2010). Hypoglycemia is increased in reduced kidney function. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, higher serum creatinine or higher urine albumin to creatinine ratio was associated with hypoglycemia requiring medical assistance (ACCORD, 2008). A recently published prospective observational study found that hypoglycemia is common among patients with CKD and type 2 diabetes; continuous glucose monitoring detected glucose ≤ 70 mg/dL in 76% (61/80) and glucose ≤ 60 mg/dL in 61% (49/80); 39% (31/80) experienced a prolonged hypoglycemic event (glucose ≤ 54 mg/dL for 120 consecutive minutes) (Hong et al., 2020).

In recent years, large clinical trials have shown exciting benefits of newer glucose-lowering medications on cardiovascular and kidney outcomes in patients with type 2 diabetes with CKD, in addition to lowering blood glucose. Clinical trials of CANVAS, CREDENCE, EMPA-REG, DECLARE–TIMI 58, and DAPA-CKD demonstrate benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) ((Neal et al., 2017; Mahaffey et al., 2019; Zinman et al., 2015; Wiviott et al., 2019; Heerspink et al., 2020). The benefits of glucagon-like peptide-1 receptor agonists (GLP-1RA) on cardiovascular or kidney outcomes have been showed in several large clinical trials:

HARMONY, REWIND, SUSTAIN-6, LEADER, and ELIXA (Hernandez et al., 2018; Gerstein et al., 2019; Marso et al., 2016; Pfeffer et al., 2015). The risk of hypoglycemia was generally low with SGLT2i or GLP-1RA in these clinical trials. In the CANVAS trial, hypoglycemia occurred in 50.0 versus 46.4 per 1000 patient-years in the canagliflozin versus placebo groups. In the REWIND trial, the proportion of patients with severe hypoglycemia was 1.3% in the dulaglutide group versus 1.5% in the placebo group. Evidence supporting effectiveness and safety of dipeptidyl peptidase 4 inhibitors (DPP4i) in CKD patients is increasing, too. A study by Ferreira et al compared sitagliptin and glipizide on glucose lowering in patients with moderate-to-severe CKD in a randomized clinical trial, and demonstrated efficacy and lower incidence of hypoglycemia of sitagliptin (Ferreira et al., 2013).

The Kidney Disease: Improving Global Outcomes (KDIGO) provides more specific clinical guidelines for patients with CKD and type 2 diabetes. In 2021 KDIGO guideline, metformin and a SGLT2i are recommended as first-line treatment choices for CKD patients with estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min/1.73 m^2. A SGLT2i is also recommended as second-line treatment in these patients. In patients with CKD and type 2 diabetes who have not achieved individualized glycemic targets despite use of metformin and a SGLT2i, or who are unable to use those medications, a GLP-1RA is recommended (KDIGO, 2021).

Sulfonylureas are widely used as a diabetes treatment because they effectively lower blood glucose and HbA1c and they are available as generics. The second-generation agents (glyburide, glipizide, glimepiride) have largely replaced first generation drugs (chlorpropamide, tolazamide, tolbutamide) in the general population

due to lower risk of hypoglycemia. While benefits of SGLT2i and GLP-1RA among patients with type 2 diabetes and CKD have been demonstrated, there is no evidence of cardiovascular and kidney benefits of old glucose-lowering medications like sulfonylureas in this population. A real-word study comparing SGLT2i vs. sulfonylureas among patients with type 2 diabetes suggested that SGLT2i treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas (Xie et al., 2021). A meta-analysis of randomized controlled trials examined efficacy and safety of newer glucose-lowering medications. The study compared SGLT2i with sulfonylureas as second-line therapy in patients with type 2 diabetes inadequately controlled on metformin. The study included five trials involving 4,300 participants, and found that SGLT2i was associated with less hypoglycemia compared to sulfonylureas as add-on therapy to metformin (odds ratio [OR]:0.12; 95% confidence interval [CI]: 0.07-0.21) (Chen et al., 2019).

Several analyses of glucose-lowering medication class use in the general population are available. A retrospective analysis using 2015-2019 data from the Optum Clinformatics Data Mart suggested that prescription of SGLT2i was low but increasing in commercially insured patients with type 2 diabetes. Furthermore, the study showed that there were racial/ethnic, gender, and socioeconomic disparities in receipt of SGLT2i therapy. SGLT2i use was lower in Black and female patients as well as those with lower socioeconomic status (Eberly et al., 2021). Using a similar cohort design and the same dataset, McCoy et al examined adult patients (≥18 years) with type 1 or 2 diabetes for use of SGLTi2 treatment between 2013 and 2016. They showed that SGLT2i users were younger, and SGLT2i were prescribed less frequently to women versus men, and Black

versus White patients (McCoy, et al., 2019). Sumarsono et al published trends in and expenditures of glucose-lowering medications among US Medicare beneficiaries with type 2 diabetes, 2012-2017. Metformin use increased over the study timeframe and was the most commonly prescribed glucose-lowering medication, while amylin analogues were the least commonly prescribed glucose-lowering medication class (Sumarsono et al., 2020). Using Medical Expenditure Panel Survey data (MEPS) from 2008 to 2015, Raval et al examined trends in glucose-lowering medication use among US individuals with diabetes, and showed similar results (Raval et al., 2020)

There is a substantial need to update current utilization of glucose-lowering medications in CKD patients and to understand how sociodemographic and clinical factors are associated with initiation of these newer glucose-lowering prescriptions. Also, there is limited information on hypoglycemia risk from a large population perspective of newer glucose-lowering medications in CKD patients with type 2 diabetes. Data from clinical trials is based on selected populations. It is important to assess whether the results of these clinical trials are applicable to CKD patients in routine clinical practice. Also, clinical trials of SGLT2i and GLP-1RA included CKD patients, but the majority were conducted in patients with eGFR $\geq$ 30 ml/min per 1.73 m^2. There is limited data on hypoglycemia risk of these agents among patients with type 2 diabetes and CKD stages 4-5.

Health disparities in Blacks with diabetes and CKD has been well demonstrated. A cohort study with 4,251 participants found that the chance of developing diabetes was significantly higher for Black than for White adults (about 66 more cases of diabetes per 1,000 people) (Bancks et al., 2017). A large cohort study in multiethnic patients free of

cardiovascular disease and eGFR >60 ml/min per 1.73 m^2 at baseline found that kidney function decline varied significantly by race/ethnicity. Blacks had a significantly higher rate of kidney function decline than whites (0.31 ml/min per 1.73 m^2/year faster on average, p = 0.001) after adjusting for multiple potential confounders (Peralta et al., 2011). USRDS 2020 annual data reported that the adjusted prevalence of ESKD was 3.4 times higher in Blacks than Whites in 2018 (USRDS, 2020). Currently, there is little information on comparative hypoglycemia risk of newer glucose-lowering prescriptions versus sulfonylureas in different race, age, gender, or socioeconomic groups among CKD patients with type 2 diabetes.

1.3 Study aims

To address the current knowledge gap with newer glucose-lowering medications in real-world data, this study evaluated three aims:

Aim 1: To update prevalence of glucose-lowering medications in CKD patients with type 2 diabetes.

1.1. To examine current trends in utilization of individual glucose-lowering medications and distinct therapeutic classes in CKD patients with type 2 diabetes.

1.2. To examine which mono- and combination therapies are commonly prescribed for CKD patients with type 2 diabetes.

1.3. To examine patterns of glucose-lowering medication utilization in these patients by CKD stage.

Aim 2: To examine disparities in initiation of SGLT2i or GLP-1RA versus sulfonylureas (2nd generation) in CKD patients with type 2 diabetes.

2.1. To examine distribution of sociodemographic and clinical factors between SGLT2i or GLP-1RA versus sulfonylureas (2nd generation) in CKD patients with type 2 diabetes.

2.2. To investigate association of sociodemographic and clinical factors with initiation of SGLT2i or GLP-1RA versus sulfonylureas (2nd generation) in CKD patients with type 2 diabetes.

Aim 3: To compare hypoglycemia risk between newer glucose-lowering medications and sulfonylureas in CKD patients with type 2 diabetes.

3.1. To examine the risk of hypoglycemia comparing SGLT2i or GLP-1RA with sulfonylureas (2nd generation) in CKD patients with type 2 diabetes.

3.2. To examine the risk of hypoglycemia in CKD patients with type 2 diabetes across race, age, gender and socioeconomic subgroups.

Chapter 2. Literature review

The following literature review provides the context for our research questions. Section 2.1 illustrates hypoglycemia risk of glucose-lowering therapies, and hypoglycemia risk in the chronic kidney disease (CKD) population while Section 2.2 describes each glucose-lowing medication class and reviews clinical studies related to individual glucose-lowering medications with a focus on studies in the CKD population.

Currently there are twelve classes of glucose-lowering medications on the US market (Table 2.1): biguanides, sulfonylureas, meglitinides/glinides, thiazolidinediones (TZD), alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium-glucose cotransporter inhibitors (SGLT2i), incretin mimetics/glucagon-like peptide-1 receptor agonists (GLP-1RA), bile acid sequestrants, dopamine-2 agonists, amylin mimetics, and insulins (American Diabetes Association [ADA], 2018).

The Kidney Disease: Improving Global Outcomes (KDIGO) provides more specific clinical guidelines for patients with CKD and type 2 diabetes. In the 2021 KDIGO guidelines, metformin and a SGLT2i are recommended as first-line treatment choices for CKD patients with estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. A SGLT2i is also recommended as second-line treatment in these patients. In patients with CKD and type 2 diabetes who have not achieved individualized glycemic targets despite use of metformin and a SGLT2i, or who are unable to use those medications, a GLP-1RA is recommended (KDIGO, 2021).

Table 2.1. Glucose-lowering medication classes and medications

Glucose-Lowering Medication Class	Medication
Biguanides	Metformin
Sulfonylureas	
First generation	Chlorpropamide
	Tolazamide
	Tolbutamide
Second generation	Glyburide
	Glipizide
	Glimepiride
Meglitinides (glinides)	Repaglinide
	Nateglinide
Thiazolidinediones	Pioglitazone
	Rosiglitazone
Alpha-glucosidase inhibitors	Acarbose
	Miglito
Amylin mimetics	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine-2 agonists	Bromocriptine
Dipeptidyl peptidase-4 inhibitors	Sitagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
Sodium glucose cotransporter-2 inhibitors	Canagliflozin
	Dapagliflozin
	Empagliflozin
	Ertugliflozin
Glucagon-like peptide-1 receptor agonists	Exenatide/ Exenatide extended release
	Liraglutide
	Albiglutide
	Lixisenatide
	Dulaglutide
	Semaglutide
Insulins	Rapid-acting analogs
	- Lispro
	- Aspart
	- Glulisine
	Short-acting
	- Human Regular
	Intermediate-acting
	- Human NPH, neutral protamine hagedorn
	Basal insulin analogs
	- Glargine
	- Detemir
	- Degludec

2.1 Hypoglycemia

Defining hypoglycemia. While the International Hypoglycemia Study Group recommended proposed glucose levels when reporting hypoglycemia in clinical trials in 2016 (International Hypoglycemia Study Group, 2016), the ADA 2017 edition of Standards of Medical Care in Diabetes defined a blood glucose ≤ 70 mg/dL (3.9 mmol/L) as a hypoglycemia alert value (level 1), a blood glucose < 54 mg/dL (3.0 mmol/L) as serious, clinically significant hypoglycemia (level 2), and the presence of severe cognitive impairment requiring external assistance as severe hypoglycemia (level 3) for clinical practice (ADA, 2017).

Summary of reported hypoglycemia events in large clinical studies evaluating intensive therapy with glucose-lowering medications. Intensive therapies in these clinical studies mainly included older glucose-lowering medications to achieve the target glycated hemoglobin level. The UKPDS 73 trial of intensive glucose-lowering therapy in type 2 diabetes analyzed self-reported hypoglycemia (Wright et al., 2006). A total of 5,063 patients were randomized to diet alone, sulfonylurea, metformin (overweight subjects only), or insulin monotherapy therapy over 6 years from diagnosis of type 2 diabetes. Self-reported hypoglycemic episodes were categorized as (1) transitory symptoms not affecting normal activity, (2) temporarily incapacitated but patient able to control symptoms without help, (3) incapacitated and required assistance to control symptoms, and (4) required medical attention or glucagon injection, recording the most severe episode each quarter. The overall proportion of patients reporting at least one Grade 1–4 hypoglycemic episode per year was 11.0% (95% confidence interval [CI]: 10.7 to 11.2), for a Grade 2–4 episode 2.5% (2.4 to 2.7), and for a Grade 3 or 4 episode

0.55% (0.50 to 0.60). The proportion of patients reporting Grade 2–4 episodes were 0.1% on diet, 0.3% on metformin, 1.2% on sulfonylureas, 3.8% on basal insulin alone, and 5.5% on basal plus prandial insulin (Wright et al., 2006).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to evaluate effects of intensive glucose lowering therapy (reducing a glycated hemoglobin [HbA1c] level to below 6.0%) in patients with type 2 diabetes at high cardiovascular disease risk (ACCORD, 2008). A total of 10,251 patients were enrolled in the study and followed for a mean of 3.5 years. Glucose-lowering medications included metformin, sulfonylureas, TZD, and insulin. The study didn't identify benefits in reduce major cardiovascular events, but reported higher cardiovascular and all-cause mortality in the intensive-therapy group. Also, the intensive-therapy group had significantly higher rates of hypoglycemia. The annualized rate of hypoglycemic episodes requiring medical assistance was 3.1% in the intensive-therapy group and 1.0% in the standard-therapy group (ACCORD, 2008).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was also designed to evaluate effects of intensive glucose lowering therapy in patients with type 2 diabetes (ADVANCE, 2008). Intensive therapy targeted HbA1c value to 6.5% or less. Glucose-lowering medications included metformin, sulfonylureas, TZD, acarbose, glinide, and insulin. A total of 11,140 patients were enrolled in the study and followed for a median of 5 years. Intensive control reduced the incidence of combined major macrovascular and microvascular events. However, severe hypoglycemia (requiring help from another person) was more common in the intensive-control group (2.7% vs. 1.5% in the standard-control group; hazard ratio

[HR]: 1.86; 95% CI, 1.42-2.40; $p < 0.001$). On average, the rate of severe hypoglycemic events was 0.7 event per 100 patients per year in the intensive-control group and 0.4 event per 100 patients per year in the standard-control group. Minor hypoglycemia also occurred more frequently in patients undergoing intensive control (120 events per 100 patients per year, vs. 90 with standard control). Approximately 47% of patients in the intensive-control group and 62% of those in the standard-control group remained free of any hypoglycemic event during the follow-up period (ADVANCE, 2008).

The Veterans Affairs Diabetes Trial (VADT) enrolled 1791 military veterans with type 2 diabetes (median follow-up, 5.6 years), and compared the effects of intensive and standard glucose control on cardiovascular events. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in HbA1c. Glucose-lowering medications included metformin, sulfonylureas, TZD, and insulin. Hypoglycemia episodes occurred more in the intensive-therapy group (17.6%) than in the standard-therapy group (24.1%) ($p < 0.001$) (Duckworth, 2009).

***Hypoglycemia risk in CKD patients*.** Kidneys play an important role in glucose hemostasis through kidney tubular glucose absorption and gluconeogenesis (Gerich, 2010). Hypoglycemia is increased in reduced kidney function, and common in patients with type 2 diabetes and CKD. In the ACCORD trial, higher serum creatinine or higher urine albumin to creatinine ratio was associated with hypoglycemia requiring medical assistance (ACCORD, 2008). Recently, two prospective observational studies examined hypoglycemia in patients with type 2 diabetes and CKD. The first study evaluated 81 participants with CKD, defined as estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2, over 890 total days with continuous glucose monitoring. There were

255 episodes of level 1 hypoglycemia (< 70 mg/dl), of which 68 episodes reached level 2 hypoglycemia (< 54 mg/dl). Median rate of hypoglycemic episodes was 5.3 (interquartile range, 0.0-11.7) per 30 days (Ahmad et al., 2019). The second study enrolled a total of 80 patients with type 2 diabetes and eGFR < 45 ml/min per 1.73 m^2 for a mean of 12.7±2.9 days, with 80% completing the full 14 days. Patients on dialysis were excluded. The study reported that hypoglycemic events occurred in 61 of 80 patients (76%) with glucose < 70 mg/dl, and 49 of 80 (61%) with glucose < 60 mg/dl. The mean number of hypoglycemic events per patient was 7.5±9.0 when defined as glucose < 70 mg/dl, and 7.3±6.9 when defined as glucose < 60 mg/dl (Hong et al., 2020).

2.2 Glucose-lowering medications

The following section describes dosing adjustments of glucose-lowing medications, class benefits and class-related hypoglycemia events as well as provides a review of clinical studies of individual glucose-lowering medications with focus on studies in the CKD population.

Newer glucose-lowering medications

Dipeptidyl peptidase-4 inhibitors. DPP-4i block dipeptidy1 peptidase-4, an enzyme that degrades glucagon-like peptide-1. This class of medications increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, increases sense of fullness, and slows gastric emptying (ADA, 2018). Four DPP-4i are available in the current US market: alogliptin (approved 2013), linagliptin (approved 2011), saxagliptin (approved 2009), sitagliptin (approved 2006). Linagliptin is eliminated

predominantly via the bile, and hence does not require dose adjustment for CKD patients. In contrast, all other drugs in this class (sitagliptin, saxagliptin, alogliptin) are excreted mainly by the kidneys, and need dose adjustment with various degrees of kidney function. These four agents have been shown to be effective at lowering HbA1c level and safety in patients with CKD in clinical studies. And large clinical trials indicate cardiovascular safety of DPP-4 inhibitors in CKD patients. Detailed information is described below.

Sitagliptin. Several small randomized studies have shown effective glycemic control and low hypoglycemia risk of sitagliptin in CKD patients with type 2 diabetes. A 54-week study by Chan et al. enrolled 91 chronic kidney insufficiency patients with type 2 diabetes (HbA1c values of 6.5-10%). Definition of moderate kidney insufficiency was creatinine clearance (CrCl) ≥ 30 to < 50 ml/min and not on dialysis; severe kidney insufficiency was CrCl < 30 ml/min including patients with ESKD on dialysis. Patients were allocated (2:1) to sitagliptin (for 54 weeks) (50 mg daily for moderate kidney insufficiency and 25 mg daily for severe kidney insufficiency) or the sequence of placebo (for 12 weeks) followed by active treatment with glipizide (for 42 weeks). Hypoglycemia (including those not requiring assistance; those requiring the (non-medical) assistance of others; and those requiring medical intervention or exhibiting markedly depressed level of consciousness, loss of consciousness or seizure) was lower in the sitagliptin group (3/65, 4.6%) compared with the placebo/glipizide group (6/26, 23.1%) (Chan et al., 2008). Another 54-week study enrolled 426 patients with type 2 diabetes and moderate (eGFR ≥30 to <50 mL/min/1.73 m^2) or severe (eGFR <30 mL/min/1.73 m^2) kidney insufficiency. Patients were randomized to sitagliptin (50 mg daily for moderate kidney

insufficiency and 25 mg daily for severe kidney insufficiency) or glipizide. There was a lower incidence of symptomatic hypoglycemia events with sitagliptin (13/210, 6.2%) versus glipizide (36/212, 17%) ($p = 0.001$) (Ferreira, et al., 2013). Another 54-week study enrolled 129 end-stage-kidney-disease (ESKD) patients with type 2 diabetes (HbA1c level of 7-9%). Patients were randomly assigned to sitagliptin 25 mg daily or glipizide. Both sitagliptin and glipizide groups showed reduced HbA1c levels from baseline: -0.72% (95% CI, -0.95% to -0.48%) with sitagliptin and -0.87% (95% CI, -1.11% to -0.63%) with glipizide, for a difference of 0.15% (95% CI, -0.18% to 0.49%). But, the incidence of severe hypoglycemia was significantly lower in the sitagliptin group (0%) versus placebo (7.7%) (Between-group difference, -7.8% [95% CI, -17.1% to -1.9%]). The incidence of symptomatic hypoglycemia was also lower in the sitagliptin group (6.3%) versus the glipizide group (10.8%) (Between-group difference, -4.8% [95% CI, -15.7% to 5.6%]) (Ferreira, et al., 2013).

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) assessed the long-term cardiovascular safety of sitagliptin in patients with type 2 diabetes. The study included patients with an eGFR $\geq$ 30 ml/min per 1.73 m^2. A total of 14,671 patients were randomly assigned to either sitagliptin at a dose of 100 mg daily (or 50 mg daily if the baseline eGFR 30 to < 50 ml/min per 1.73 m^2) or placebo to their existing therapy and followed for a median of 3.0 years. At baseline, 9.4% on sitagliptin and 9.3% on placebo had an eGFR < 50 ml/min per 1.73 m^2. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. The study showed that sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (HR: 0.98;

95% CI: 0.88-1.09; $p < 0.001$ for noninferiority). For kidney outcomes, at 48 months, the mean eGFR reduction from baseline was greater in the sitagliptin group than in the placebo group (−4.0±18.4 and −2.8±18.3 ml/min per 1.73 m^2, respectively). Kidney function declined in both the sitagliptin and placebo groups, but the slightly lower eGFR value remained consistent in the sitagliptin group over all visits. There was no significant difference between the sitagliptin group (2% [144 patients]) and the placebo group (1.7% [125 patients]) with respect to severe hypoglycemia (Green et al., 2015).

Saxagliptin. A 52-week study enrolled 170 adults with type 2 diabetes (with HbA1c 7-11%) and creatinine clearance < 50 ml/min or ESKD. Patients were randomized to saxagliptin 2.5 mg once daily or placebo. The study showed effective glycemic control and safety of saxagliptin in patients with type 2 diabetes and kidney impairment. Proportions of hypoglycemia were 29% in the saxagliptin versus 28% in the placebo group (Nowicki, et al., 2011).

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial enrolled 16,492 patients with type 2 diabetes. Patients were randomized to saxagliptin versus placebo and followed for a median of 2.1 years. A total of 13,916 (84.4%) had normal or mildly impaired kidney function (eGFR > 50 ml/min per 1.73 m^2), 2,240 (13.6%) had moderate kidney impairment (eGFR 50-30 ml/min per 1.73 m^2), and 336 (2.0%) had severe kidney impairment (eGFR < 30 ml/min per 1.73 m^2). The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke, and occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (HR: 1.00; 95% CI: 0.89-1.12; $p < 0.001$ for noninferiority) (Scirica et al., 2013).

But, treatment with saxagliptin was associated with a reduction in albumin/creatinine ratio (ACR) compared with placebo: the difference in mean change in ACR at 2 years was -34.3 mg/g ($p < 0.004$), mainly driven by the difference in change in ACR among patients with ACR > 300 mg/g at baseline (-283 mg/g; $p = 0.002$) (Mosenzon et al., 2017).

The SAVOR-TIMI 53 trial reported more detailed information on events of hypoglycemia. Hospitalization for hypoglycemia occurred infrequently, and the rate was similar in the two groups: 0.6% (53 patients) in the saxagliptin group and 0.5% (43 patients) in the placebo group (HR with saxagliptin, 1.22; 95% CI, 0.82-1.83; $p = 0.33$). However, the study reported a higher proportion of at least one hypoglycemic event (minor or major) in in the saxagliptin group than the placebo group (15.3% vs. 13.4%, $p < 0.001$); minor hypoglycemia (the patients had symptoms but recovered without assistance within 30 minutes after ingestion of carbohydrates) 14.2% in the saxagliptin group vs. 12.5% in the placebo group ($p = 0.002$); major hypoglycemia (the events required a third party to intervene actively) 2.1% of saxagliptin-treated patients vs. 1.7% in placebo group ($p = 0.047$) (Scirica et al., 2013).

Linagliptin. A 1-year study enrolled 133 patients with type 2 diabetes (HbA1c 7.0–10.0%) and severe kidney impairment (eGFR < 30 ml/min per 1.73 m^2). Patients were randomized to linagliptin 5 mg or placebo once daily. The study showed that HbA1c improvements were sustained with linagliptin (−0.71%) over placebo (0.01%) at 1 year (treatment difference −0.72%, −1.03 to −0.41; $p < 0.0001$). Risk of severe hypoglycemia with linagliptin was very low (McGill et al., 2013).

Several other clinical studies showed similar results of linagliptin on effective glycemic control and safety in patients with type 2 diabetes and kidney impairment (Groop et al., 2013; Groop et al., 2014; McGill et al., 2014; McGill et al., 2015). The Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAgliptin (MARLINA-T2D) study was designed to investigate albuminuria-lowering effects of linagliptin. The study enrolled 360 individuals with type 2 diabetes (HbA1c 6.5% to 10.0%), eGFR ≥ 30 ml/min per 1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) 30–3000 mg/g. Patients were randomized to receive linagliptin 5 mg daily or placebo for 24 weeks. The study demonstrated that linagliptin significantly improved glycemic control. Investigator-reported hypoglycemia occurred in 24 linagliptin-treated participants (24/182, 13.2%) and in 10 participants receiving placebo (10/178, 5.6%). Most hypoglycemia happened in those receiving concomitant treatment with sulfonylureas or insulin (Groop et al., 2017).

The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) study was designed to evaluate effects of linagliptin on cardiovascular and kidney outcomes (Rosenstock et al., 2019). The study enrolled 6,979 patients with type 2 diabetes (HbA1c 6.5–10.0%). Individuals with baseline eGFR <15 ml/min per 1.73 m^2 were excluded. Patients were randomized to receive once-daily oral treatment with linagliptin 5 mg or matching placebo and followed for a median of 2.2 years. Mean eGFR was 54.6 ml/min per 1.73 m^2, and 15% participants had severe renal impairment (eGFR < 30 and > 15 ml/min per 1.73 m^2). The primary outcome was the time to first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The key secondary outcome was a composite

of time to first sustained occurrence of end-stage kidney disease, ≥ 40% decrease in eGFR from baseline, or kidney death. The study demonstrated noninferiority of linagliptin versus placebo with regard to risk of major cardiovascular events (HR, 1.02; 95% CI, 0.89-1.17; $p < 0.001$ for noninferiority). The risk of the secondary kidney composite outcome was not significantly different between linagliptin and placebo (HR, 1.04; 95% CI, 0.89-1.22; $p = 0.62$). Proportions of hypoglycemia events with linagliptin vs placebo were: investigator-reported events 29.7% (1,036) and 29.4% (1,024); confirmed hypoglycemic adverse events with plasma glucose < 54 mg/dL (< 3.0 mmol/L) or severe events 15.9% (557) and 16.4% (575); severe events 3.0% (106) and 3.1% (108), respectively. A numerically higher rate of hypoglycemia was observed with linagliptin compared with placebo in patients taking sulfonylurea at baseline (15.5 per 100 person-years compared with placebo, 13.7 per 100 person-years) (Rosenstock et al., 2019).

Alogliptin. Two small studies evaluated efficacy of alogliptin in patients with type 2 diabetes and with CKD. A 2-year study enrolled 16 diabetic hemodialysis patients (HbA1c level > 6.5%) (Nakamura et al., 2013). The other, a 48-week study, enrolled 30 patients with type 2 diabetes who were undergoing hemodialysis (Fujii et al., 2013). Both of the studies demonstrated alogliptin improved glycemic control and was generally well tolerated in patients with hemodialysis.

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial was designed to evaluate cardiovascular outcomes with alogliptin in patients with type 2 diabetes who are at very high cardiovascular risk. A total of 5,380 patients randomly received alogliptin or placebo and followed for up to 40 months. At baseline, 29.6% on alogliptin and 28.6% on placebo had an eGFR < 60 ml/min per 1.73

m^2. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The study demonstrated cardiovascular safety of alogliptin (HR: 0.96; upper boundary of the one-sided repeated CI, 1.16; $p < 0.001$ for noninferiority). The incidence of hypoglycemia was similar in the alogliptin and placebo groups: any hypoglycemia (181/2,701, 6.7% vs. 173/2,679, 6.5%; $p = 0.74$); serious hypoglycemia (18/2,701, 0.7% vs 16/2,679, 0.6%; $p = 0.86$) (White et al., 2013).

Summary. A summary of these study results is found in Table 2.2. All the studies demonstrated cardiovascular safety of DPP-4i, but did not show evidence of cardiovascular benefit. Also, there was no evidence of significant benefit for kidney outcomes, except for saxgliptin. Because of good efficacy in lowering blood glucose and safety, this class of agents presents a treatment choice in patients with type 2 diabetes and CKD. Clinical studies showed that DPP-4i were effective and safe in patients receiving hemodialysis with a reduced dose, except for linagliptin, which does not require dose adjustment. DPP-4i might be the favored choice among CKD stages 4-5 patients. We anticipate that sitagliptin use might be higher in CKD patients than other DPP-4 inhibitors due to being on the market longer.

Table 2.2. Summary of large clinical studies assessing DDP-4 inhibitors in CKD patients with type 2 diabetes

DPP-4 inhibitors	Clinical trial	Total of participants	Percent with CVD	Percent with eGFR < 60 ml/min per 1.73 m^2	Kidney function eligibility criteria	Primary outcome	cardiovascular outcomes /effect	Kidney outcomes/effect	Hypoglycemia
Sitagliptin	TECOS	14,671	100%	9.4% with eGFR < 50 mL/min per 1.73 m^2	eGFR ≥ 30 mL/min per 1.73 m^2	Cardiovascular outcomes	MACE, or hospitalization for unstable angina: ⟺	The mean eGFR: marginally lower in sitagliptin group.	Severe: ⟺
Saxagliptin	SAVOR-TIMI 53	16,492	78.6%	15.6% with eGFR < 50 mL/min per 1.73 m^2	eGFR ≥ 15 mL/min per 1.73 m^2	MACE	MACE: ⟺	albumin/creatinine ratio (ACR): ⇓	Minor or major: ⇑
Linagliptin	CARMELINA	6,979	NA	62.3%	eGFR ≥ 15 mL/min per 1.73 m^2	MACE	MACE: ⟺	A composite kidney outcome: ⟺	⟺
Alogliptin	EXAMINE	5,380	100%	29%	NA	MACE	MACE: ⟺	NA	⟺

Note: CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MACE, a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Glucagon-like peptide-1 receptor agonist or incretin memetic. GLP-1RA treatment enhances insulin secretion in response ingestion of food, decreases glucagon secretion, slows gastric emptying, and increases sense of fullness (ADA, 2018). GLP-1RA include albiglutide (approved 2014), dulaglutide (approved 2014), exenatide (approved 2005) and exenatide extended-release (approved 2012), liraglutide (approved 2010), lixisenatide (approved 2016), semaglutide (approved 2017). Most current GLP-1RA are injectable. The first oral GLP-1RA, semaglutide, was approved in 2019 by the US Food and Drug Administration (FDA). In addition to efficacy of lowering blood glucose and safety, recently large clinical studies have demonstrated cardiovascular or kidney benefits of GLP-1RA in patients with type 2 diabetes and CKD. The detailed evidence of these studies are showed the below.

Albiglutide. The HARMONY trial enrolled 9,463 participants with type 2 diabetes and cardiovascular disease. Participants were randomly assigned to receive subcutaneous injections of albiglutide or placebo once a week and followed for a median of 1.6 years. The baseline eGFR enrollment criteria was ≥ 30 ml/min per 1.73 m^2. And the mean eGFR was 79 ml/min per 1.73 m^2. The primary outcome was the first occurrence of cardiovascular death, myocardial infarction, or stroke. The risk of the primary composite outcome was lower with albiglutide than with placebo (HR: 0.78; 95% CI: 0.68–0.90). The proportion of patients with severe hypoglycemia was 1% (31/4717) in the albiglutide group versus 1% (55/475) in the placebo group (Hernandez et al., 2018).

Dulaglutide. The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial enrolled 9,901 participants with type 2 diabetes

(HbA1c<9.5%). Participants were randomly assigned to weekly subcutaneous injections of either dulaglutide 1.5 mg or placebo and followed for a median of 5.4 years. Patients with an eGFR < 15 ml/min per 1.73 m^2 were excluded from the study. 31.5% participants reported previous cardiovascular disease and 22.2% had a baseline eGFR < 60 mL/min per 1.73 m^2. The median eGFR was 74.9 ml/min per 1.73 m^2. The primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) was significantly lower with once-weekly dulaglutide compared to placebo (HR: 0.88; 95% CI: 0.79–0.99) (Gerstein et al., 2019 cardiovascular). The REWIND trial also examined dulaglutide's benefit on kidney outcomes (Gerstein et al., 2019 renal). The kidney composite outcome, which was defined as the first occurrence of new macroalbuminuria (UACR > 33.9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic kidney replacement therapy, was lower in the dulaglutide group than the placebo group (HR: 0.85; 95% CI: 0.77–0.93). And there was a significant reduction in new macroalbuminuria (HR: 0.77; 95% CI: 0.68–0.87). The proportion of patients with severe hypoglycemia was 1.3% (64/4,949) in the dulaglutide group versus 1.5% (74/4,952) in the placebo group (Gerstein et al., 2019 cardiovascular).

The AWARD-7 trial assessed the efficacy and safety of dulaglutide in patients with type 2 diabetes (HbA1c of 7.5-10.5%) and moderate-to-severe chronic kidney disease (stage 3-4). A total of 577 patients were randomly to receive once-weekly dulaglutide 1.5 mg, once-weekly dulaglutide 0.75 mg, or daily titrated insulin glargine. The mean eGFR was 38 ml/min per 1.73 m^2. The primary outcome was HbA1c. Secondary outcomes included eGFR and urine albumin-to-creatinine ratio (UACR). The trial showed dulaglutide's efficacy in glycemic control and safety in patients with

moderate-to-severe CKD. And the trial also showed potential kidney benefits of dulaglutide. The reduction in eGFR was greater over the study time period with insulin glargine vs dulaglutide groups. Similar to the REWIND trial, patients with hypoglycemia was less common in the AWARD-7 trial. Hypoglycemia events (defined as plasma glucose concentration ≤70 mg/dL [3.9 mmol/L]) occurred in 3 (2%) of 192 with dulaglutide 1.5 mg, 9 (5%) of 190 with dulaglutide 0.75 mg, 16 (8%) of 194 with insulin glargine; overall p = 0.01 (Tuttle et al., 2018).

Semaglutide. The semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial enrolled 3,297 patients with type 2 diabetes. Patients were randomly assigned to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo and followed for a median of 2.1 years. Of the 3,297 patients, 83.0% (2,735) had established cardiovascular disease (including CKD stage 3 or higher). The primary outcome (defined as the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 108 of 1,648 patients (6.6%) in the semaglutide group and in 146 of 1,649 patients (8.9%) in the placebo group (HR: 0.74; 95% CI: 0.58–0.95). There was also a reduction of new or worsening nephropathy (including persistent macroalbuminuria, persistent doubling of serum creatinine level and a creatinine clearance of < 45 ml/min per 1.73 m2, or need for kidney replacement therapy) in the semaglutide group (HR: 0.64; 95% CI: 0.46–0.88). And this reduction was largely driven by reductions in persistent macroalbuminuria (HR: 0.54; 95% CI: 0.37-0.77). Any hypoglycemia (severe or symptomatic events) occurred in 21.7% of semaglutide 1.0 mg, 23.1% of semaglutide 0.5 mg, 21.0% in 1.0 mg placebo, 21.5% in 0.5 mg placebo groups in the SUSTAIN-6 trial (Marso et al., 2016).

Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial examined cardiovascular risk with oral semaglutide among patients with type 2 diabetes. A total of 3,183 patients were randomly assigned to receive oral semaglutide or placebo and followed for a median of 15.9 months. The mean eGFR at baseline was 74 ml/min per 1.73 m^2. And 84.7% had established cardiovascular disease or CKD. The baseline eGFR enrollment criteria was ≥ 30 ml/min per 1.73 m^2 but there were 0.9% (29 patients) with eGFR < 30 ml/min per 1.73 m^2. The primary outcome, which was the first occurrence of a major adverse cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), occurred in 61 of 1,591 patients (3.8%) in the oral semaglutide group and 76 of 1,592 (4.8%) in the placebo group (HR: 0.79; 95% CI: 0.57-1.11; $p < 0.001$ for noninferiority). The study showed that cardiovascular risk of oral semaglutide was not inferior to that of placebo. Severe hypoglycemia was 1.4% (23) in oral semaglutide group and 0.8% (13) in the placebo group (Husain et al., 2019).

Liraglutide. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial enrolled a total of 9,340 patients with type 2 diabetes and followed for a median of 3.8 years. The baseline eGFR enrollment criteria was ≥ 30 ml/min per 1.73 m^2 but there were 2.4% with eGFR < 30 ml/min per 1.73 m^2. Patients were randomly assigned to receive either liraglutide or matching placebo once daily as a subcutaneous injection. At baseline, 81.3% had established cardiovascular disease. The primary outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in significantly fewer patients in the liraglutide group (608 of 4,668 patients [13.0%]) than in the placebo group (694 of 4,672 [14.9%]) (HR: 0.87; 95% CI: 0.78–0.97) (Marso et al., 2016). The secondary kidney outcome also

occurred in fewer participants in the liraglutide group than in the placebo group (268 of 4,668 patients vs. 337 of 4,672; HR: 0.78; 95% CI: 0.67-0.92). The kidney outcome was a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage kidney disease, or death due to kidney disease. Similar to other GLP-1 trials, this kidney composite outcome result was driven primarily by reduction of the new onset of persistent macroalbuminuria (HR: 0.74; 95% CI: 0.60-0.91) (Mann et al., 2017). The LEADER trial reported that confirmed hypoglycemia (plasma glucose level, < 56 mg per deciliter [3.1 mmol per liter]) occurred in 43.7% (2,039/4,668) in the liraglutide group and 45.6% (2,130/4,672) in the placebo group (rate ratio: 0.80: 95% CI: 0.74-0.88); severe hypoglycemia (for which the patient required assistance from a third party) occurred in 2.4% (114 patients) in the liraglutide group and in 3.3% (153 patients) in the placebo group (rate ratio, 0.69; 95% CI: 0.51-0.93) (Marso et al., 2016).

Lixisenatide. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial enrolled 6,068 patients with type 2 diabetes and a recent acute coronary syndrome. Patients were randomly assign to once-daily subcutaneous injections of lixisenatide or placebo and followed for a median of 25 months. The primary composite outcome was cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. The study showed noninferiority of lixisenatide to placebo ($p < 0.001$) but did not show superiority ($p = 0.81$) (HR: 1.02; 95% CI: 0.89-1.17) (Pfeffer et al., 2015). The exploratory analysis of ELIXA demonstrated a kidney benefit of lixisenatide in reducing progression of urinary albumin-to-creatinine ratio (UACR) in macroalbuminuric patients, and adjusted least-squares mean percentage change in UACR from the baseline was -39.18% (-68.53 to -9.84; $p = 0.0070$) (Muskiet et al., 2018).

Hypoglycemic episodes during the study were reported in 504 patients (16.6%) in the lixisenatide group and in 462 (15.2%) in the placebo group ($p = 0.14$). Serious hypoglycemic episodes (requiring assistance from another person) were numerically less frequent with lixisenatide (14 patients reporting 16 events) than with placebo (24 patients reporting 37 events) (Pfeffer et al., 2015).

Exenatide. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial enrolled 14,752 patients with type 2 diabetes. Patients were randomly assigned to receive subcutaneous injections of extended-release exenatide or placebo once weekly and followed for a median of 3.2 years. 73.1% had previous cardiovascular disease at baseline. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The study demonstrated cardiovascular safety of exenatide (HR: 0.91; 95% CI: 0.83-1.00; $p = 0.06$ for superiority, $p < 0.001$ for noninferiority) (Holman et al., 2017). The exploratory analysis of EXSCEL estimated effects on kidney composite 1 (40% eGFR decline, kidney replacement, or kidney death) and kidney composite 2 (composite 1 variables plus macroalbuminuria). Exenatide did not affect kidney composite 1 and 2 outcomes in unadjusted analyses, but kidney composite 2 outcome was reduced with exenatide after adjustment (HR: 0.85; 95% CI: 0.74-0.98) (Bethel et al., 2020). The rate of severe hypoglycemia when measured as the first event only was 1.0 events per 100 patient-years in the exenatide group and 0.9 events per 100 patient-years in the placebo group; when recurrent hypoglycemic events were evaluated there were 1.6 events per 100 patient-years and 1.8 events per 100 patient-years, in the exenatide and the placebo groups, respectively (Holman et al., 2017).

Summary. A summary of these study results is in Table 2.3. Three GLP-1 receptor agonists (liraglutide, dulaglutide, and semaglutide) have been shown to have benefits on cardiovascular and kidney outcomes in CKD patients. Based on these positive trial results, we anticipate that use of these agents will increase in CKD patients with type 2 diabetes

Table 2.3. Summary of large clinical studies assessing GLP-1 receptor agonists in CKD patients with type 2 diabetes

GLP-1 receptor agonists	Clinical trial	Total of participants	Percent with CVD	Percent with eGFR <60 ml/min per 1.73 m^2	Kidney function eligible for inclusion in clinical trials	Primary outcome	Cardiovascular outcomes/effect	Kidney outcomes/effect	Hypoglycemia
Albiglutide	HARMONY	9,463	100%	NA	eGFR ≥30 mL/min per 1.73 m^2	MACE	MACE: ⬇	NA	⟺
Dulaglutide	REWIND	9,901	31.5%	22.2%	eGFR ≥15 mL/min per 1.73 m^2	MACE	MACE: ⬇	A composite kidney outcome: ⬇	⟺
	AWARD-7	577	NA	100% with CKD stages 3-4	NA	HbA1c	NA	The eGFR value: ⬆	⬇
Semaglutide	SUSTAIN-6	3,297	83.0%	28.5%	NA	MACE	MACE: ⬇	New or worsening nephropathy: ⬇	⟺
	PIONEER	3,183	84.7%	26.9%	eGFR ≥30 ml/min per 1.73 m^2	MACE	MACE: ⟺	NA	⟺
Liraglutide	LEADER	9,340	81.3%	23.1%	eGFR ≥30 mL/min per 1.73 m^2	MACE	MACE: ⬇	A composite kidney outcome: ⬇	⬇
Lixisenatide	ELIXA	6,068	100%	23%	eGFR ≥30 mL/min per 1.73 m^2	Cardiovascular outcome	MACE, or hospitalization for unstable angina: ⟺	UACR: ⬇	⟺
Extended-release exenatide	EXSCEL	14,752	73.1%	22.9%	eGFR ≥30 mL/min per 1.73 m^2	MACE	MACE: ⟺	kidney composite 1: ⟺ Kidney composite 2: ⬇	⟺

Note: CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MACE, a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Sodium-glucose cotransporter 2 inhibitors or "flozins". The sodium-glucose co-transport 2 protein is located in the renal proximal tubule and is responsible for 90% of glucose reabsorption. SGLT2i block glucose reabsorption in the kidney, and increase urinary excretion of glucose (ADA, 2018). Plasma drug concentration is increased in proportion to the degree of kidney dysfunction. Currently, SGLT2i are recommended for patients with an eGFR ≥ 30 ml/min per 1.73 m^2. The SGLT2 class includes canagliflozin (approved 2013), dapagliflozin (approved 2014), empagliflozin (approved 2014), and ertugliflozin (approved 2017). Large clinical trials demonstrate safety, efficacy and beneficial effects of SGLT2 inhibitors on cardiovascular or kidney outcomes in patients with CKD and type 2 diabetes. The detailed evidence of these studies are shown below.

Canagliflozin. The Canagliflozin Cardiovascular Assessment Study (CANVAS) integrated data from two clinical trials (CANVAS and CANVAS-R) and enrolled a total of 10,142 participants with type 2 diabetes (HbA1c of 7.0% to 10.5%). The eGFR enrollment criteria was at least 30 ml/min per 1.73 m^2. Participants were randomized to canagliflozin 100 or 300 mg per day versus placebo and followed for a median of 126.1 weeks. The mean duration of diabetes was 13.5 years; 65.6% had a history of cardiovascular disease, and 20.1% had CKD with an eGFR < 60 ml/min per 1.73 m^2. The rate of the primary outcome MACE (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) was lower with canagliflozin than with placebo (HR: 0.86; 95% CI: 0.75–0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). The study also showed kidney benefits of canagliflozin versus placebo: lower risk of progression of albuminuria (HR: 0.73; 95% CI: 0.67–0.79) and lower risk of a composite kidney outcome (sustained 40% reduction in eGFR, need for kidney

replacement therapy, or death from kidney cause) (HR: 0.60; 95% CI: 0.47–0.77). In the CANVAS trial, hypoglycemia occurred in 50.0 versus 46.4 per 1000 patient-years in the canagliflozin versus placebo groups (p = 0.2) (Neal et al., 2017).

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial enrolled 4,401 patients with type 2 diabetes (HbA1c 6.5-12.0%) and the primary outcome evaluated was a kidney outcome. The patients were randomly assigned to receive either canagliflozin or placebo and followed for a median of 2.62 years. The mean glycated hemoglobin value was 8.3%; 50% of patients had established cardiovascular disease, and the mean eGFR was 56.2 ml/min per 1.73 m^2. The eGFR enrollment criteria was 30 to < 90 ml/min per 1.73 m^2 and albuminuria (urinary albumin-to-creatinine ratio, > 300 to 5000, with albumin measured in milligrams and creatinine in grams). The risk of hospitalization for heart failure (HR: 0.61; 95% CI: 0.47–0.80) and MACE (HR: 0.80; 95% CI: 0.67–0.95) was lower with canagliflozin than with placebo. The primary kidney outcome was defined as a composite of either ESKD, doubling of serum creatinine, or death from kidney or cardiovascular causes. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR: 0.70; 95% CI: 0.59–0.82). The composite endpoint without death from cardiovascular causes was also lower by 34% in the canagliflozin group (HR: 0.66; 95% CI: 0.53-0.81) (Mahaffey et al., 2019).

Empagliflozin. The EMPA-REG OUTCOME trial enrolled 7,020 patients with type 2 diabetes (HbA1c of 7.0-10.0%). The patients were randomly assigned to receive either empagliflozin or placebo and followed for a median of 3.1 years. Almost 100% had

established cardiovascular disease and 25.9% of participants had an eGFR < 60 ml/min per 1.73 m^2. The primary MACE outcome occurred in a significantly lower percentage of patients in the empagliflozin group (490 of 4,687 [10.5%]) than in the placebo group (282 of 2,333 [12.1%]) (HR: 0.86; 95.02% CI: 0.74-0.99). Hospitalization for heart failure was also lower in the empagliflozin versus placebo groups (HR: 0.65; 95% CI: 0.50–0.85) (Zinman et al., 2015). The secondary kidney microvascular outcome was incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albumin-to-creatinine ratio, > 300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an eGFR of ≤ 45 ml/min per 1.73 m^2; the initiation of kidney-replacement therapy; or death from kidney disease. Empagliflozin reduced incident or worsening nephropathy by 39% (HR: 0.61; 95% CI: 0.53 to 0.70) (Wanner et al., 2016). In the EMPA-REG OUTCOME trial, any hypoglycemia (a plasma glucose level of less than 70 mg per deciliter or a hypoglycemic event requiring assistance), occurred in 27.8% in the empagliflozin-treated patients versus 27.9% placebo groups. Severe hypoglycemia requiring third-party assistance occurred in 1.3% of empaglifozin-treated patients versus 1.5% in placebo group (Zinman et al., 2015).

The EMPEROR-Reduced trial enrolled 3,730 patients with chronic heart failure (with a left ventricular ejection fraction of 40% or less) (with or without diabetes) (Packer et al., 2020). The patients were randomly assigned to receive either empagliflozin or placebo and followed for a median of 16 months. Nearly 50% had a history of diabetes, and 48% had eGFR of less than 60 ml/min per 1.73 m^2. The primary outcome of death from cardiovascular causes or hospitalization for heart failure occurred in a significantly

lower percentage of patients in the empagliflozin group (19.4%) than in the placebo group (24.7%) (HR: 0.75; 95% CI: 0.65-0.86) (Packer et al., 2020).

Dapagliflozin. The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial evaluated 17,160 type 2 diabetes patients (HbA1c 6.5-12.0%). The patients were randomly assigned to receive dapagliflozin daily or matching placebo and followed for a median of 4.2 years. The median duration of diabetes was 11.0 years, and the mean eGFR was 85.2 ml/min per 1.73 m^2. An eGFR between 60 and 90 ml/min per 1.73 m^2 or a creatinine clearance of 60 ml or more per minute was an eGFR enrollment criterion, and only a small percentage (7%) of patients had an eGFR of less than 60 ml/min per 1.73 m^2. Dapagliflozin did not result in a lower rate of MACE (HR: 0.93; 95% CI: 0.84-1.03; p = 0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (HR: 0.83; 95% CI: 0.73-0.95; p = 0.005) (Wiviott et al., 2019). There was also a risk reduction in kidney composite outcome (≥40% decrease in eGFR to < 60 ml/min per 1.73 m^2, ESKD, or death from renal or cardiovascular causes) (HR: 0.76; 95% CI: 0.67-0.87); excluding death from cardiovascular causes, the HR was 0.53 (95% CI: 0.43-0.66) (Mosenzon et al., 2019). In the DECLARE–TIMI 58 trial, major hypoglycemia occurred in 0.7% in the dapagliflozin versus 1.0% in the placebo (HR: 0.68; 95% CI: 0.49–0.95; p = 0.02) (Wiviott et al., 2019).

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial evaluated 4,304 participants with CKD (eGFR 25–75 ml/min per 1.73 m^2 and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) ACR 200 to 5000) (with or without type 2

diabetes). Participants were randomly assigned to receive dapagliflozin or matching placebo and followed for a median of 2.4 years. The mean eGFR was 43.1 ml/min per 1.73 m^2, and 67.5% had received a diagnosis of type 2 diabetes. The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from kidney or cardiovascular causes. The risk of the primary outcome event was lower with dapagliflozin than with placebo (HR: 0.61; 95% CI: 0.51-0.72); the hazard ratio for the composite outcome, excluding cardiovascular causes, was 0.56 (95% CI: 0.45-0.68). A composite of death from cardiovascular causes or hospitalization for heart failure was also lower with dapagliflozin than with placebo (HR: 0.71; 95% CI, 0.55-0.92; p = 0.009). The DAPA-CKD trial reported similar results on major hypoglycemia (symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention): 0.7% in the dapagliflozin versus 1.3% in the placebo group (Heerspink et al., 2020).

The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial was designed to focus on patients with heart failure. A total of 4,443 patients was evaluated and followed for a median of 18.2 months. The baseline eGFR enrollment criteria was an eGFR ≥ 30 ml/min per 1.73 m^2. The mean eGFR was 66 ml/min per 1.73 m^2, and 55% of individuals was without diabetes. The study showed cardiovascular benefits of dapagliflozin and the HR for a composite of cardiovascular death, heart failure hospitalization, or urgent heart failure visit was 0.74 (95% CI: 0.65–0.85) versus placebo. Major hypoglycemia (defined as requiring assistance of another person) was rare: 0.2% with dapagliflozin and 0.2% with placebo (McMurray et al., 2019).

Ertugliflozin. The VERTIS CV clinical trial evaluated cardiovascular effects of ertugliflozin among patients with type 2 diabetes (with a glycated hemoglobin level HbA1c of 7.0 to 10.5%) and atherosclerotic cardiovascular disease. A total of 8,246 patients were randomly assigned to receive ertugliflozin or placebo once daily and followed for a mean of 3.5 years. The baseline eGFR criteria for enrollment was ≥30 ml/min per 1.73 m^2. The mean duration of diabetes was 13.0 years. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The study showed that ertugliflozin was noninferior to placebo (HR: 0.97; 95.6% CI: 0.85-1.11; $p < 0.001$ for noninferiority). With respect to the kidney outcome, the HR for death from kidney causes, kidney replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI: 0.63 to 1.04) (Cannon et al., 2020). In the VERTIS CV clinical trial, symptomatic hypoglycemia, which was defined as an event with clinical symptoms that were reported by the investigator as hypoglycemia (biochemical documentation not required), occurred in 768 (28%) in who received the 5 mg dose of ertugliflozin and in 728 patients (26.5%) who received the 15 mg dose, as compared with 790 patients (28.8%) who received placebo. Severe hypoglycemia occurred in 118 (4.3%) in the 5-mg dose of ertugliflozin, 118 (4.3%) in the 15-mg dose, and 106 (3.9%) in the placebo (Cannon et al., 2020).

Summary. A summary of these study results is presented in Table 2.4. The clinical studies showed that SGLT2 inhibitors (canagliflozin, empagliflozin, and dapagliflozin) slowed the progression of cardiac and kidney disease in patients with CKD and type 2 diabetes. Similar to trends in GLP-1RA use, we anticipate that use of these agents will increase in CKD patients with type 2 diabetes

Table 2.4. Summary of large clinical studies assessing SGLT2 inhibitors in CKD patients with type 2 diabetes

SGLT2 inhibitors	Clinical trial	Total of participants	Percent with CVD	Percent with eGFR < 60 ml/min per 1.73 m2	Kidney function eligible for inclusion in clinical trials	Primary outcome	Cardiovascular outcomes/effect	Kidney outcomes/effect	Hypoglycemia
Canagliflozin	CANVAS	10,142	65.6%	20.1%	eGFR ≥ 30 ml/min per 1.73 m^2	MACE	MACE: ⬇ Hospitalization for heart failure: ⬇	A composite kidney outcome: ⬇ Progression of albuminuria: ⬇	⟺
	CREDENCE	4,401	50%	59%	eGFR 30 to < 90 ml/min per 1.73 m^2 and UACR > 300 to 5000)	Kidney outcome	MACE: ⬇ Hospitalization for heart failure: ⬇	A composite kidney outcome: ⬇	NA
Empagliflozin	EMPA-REG	7,020	Almost 100%	25.9%	eGFR ≥ 30 ml/min per 1.73 m^2	MACE	MACE: ⬇ Hospitalization for heart failure: ⬇	Incident or worsening nephropathy: ⬇	⟺
	EMPEROR-Reduced	3,730 (50% with diabetes)	100% with heart failure	48%	eGFR ≥ 20 ml/min per 1.73 m^2	Cardiovascular outcome	Death from cardiovascular causes or hospitalization for heart failure: ⬇	NA	NA
Dapagliflozin	DECLARE–TIMI 58	17,160	40.6%	7.4%	eGFR 60-90 ml/min per 1.73 m^2 or a creatinine	Cardiovascular outcome	MACE: ⟺ Cardiovascular death or	A composite kidney outcome: ⬇	⬇

					clearance of 60 ml or more per minute.		hospitalization for heart failure (primary outcome): ⬇		
	DAPA-CKD	4,304 (67.5% with diabetes)	37%	89%	eGFR 25–75 ml/min per 1.73 m^2 and a urinary albumin-to-creatinine ratio 200 to 5000.	Kidney outcome	A composite of death from cardiovascular causes or hospitalization for heart failure: ⬇	A composite kidney outcome: ⬇	⟺
	DAPA-HF	4,443 (45% with diabetes)	100% with heart failure	43%	eGFR ≥ 30 ml/min per 1.73 m^2	Cardiovascular outcome	a composite cardiovascular outcome: ⬇	NA	⟺
Ertugliflozin	VERTIS CV	8,246	100%	22%	eGFR ≥ 30 ml/min per 1.73 m^2	MACE	MACE: ⟺	A composite kidney outcome: ⟺	⟺

Note: CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MACE, a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Older glucose-lowering medications

Biguanide (Metformin). Metformin (approved 1995) is a member of the biguanide class of glucose-lowering medications. Metformin is considered as the first-line treatment for patients with type 2 diabetes, unless there are contraindications. It lowers glucose by decreasing hepatic glucose production, intestinal absorption of glucose, and increasing insulin sensitivity in muscle and fat (ADA, 2018). Metformin is inexpensive, and effectively lowers plasma glucose. The UKPDS 34 was designed to evaluate intensive glucose control therapies (achieving a fasting glucose < 6 mmol/l (< 108 mg/dl)). Patients with newly diagnosed type 2 diabetes were allocated to receive either metformin, sulfonylureas, insulin, or the conventional therapy (primarily with diet alone) and followed for a median of 10.7 years. The study demonstrated a reduced risk of cardiovascular events and death with metformin compared with sulfonylureas, insulin, or diet restriction. Compared with the conventional group (diet restriction), patients with metformin had a risk reduction of 32% (95% CI: 13%-47%, p = 0.002) for any diabetes-related endpoint, 42% for diabetes-related death (9%-63%, p = 0.017), and 36% for all-cause mortality (9%-55%, p = 0.011). Among intensive glucose therapies, metformin also showed a greater effect than sulfonylureas or insulin on these outcomes (UKPDS 34, 1998).

However, metformin is mainly eliminated by the kidneys and is associated with risk of lactic acidosis, which has in the past limited its use in patients with CKD. In recent years, several articles have discussed that metformin can be safely used in patients with mild to moderate kidney function (Klachko & Whaley-Connell, 2011; Rachmani et al., 2002; Scarpello & Howlett, 2008). In 2016, the FDA requested a labeling change

regarding metformin use in patients with reduced kidney function (FDA, 2016). Consistent with the FDA label change, ADA guidelines state that metformin is contraindicated in patients with eGFR < 30 ml/min per 1.73 m^2 (ADA, 2017; ADA, 2018). Accordingly, the ADA and European Association for the Study of Diabetes 2019 guidelines recommend that metformin be considered as the first-line treatment for patients with type 2 diabetes with eGFR 30-60 ml/min per 1.73 m^2 (Buse et al., 2020). KDIGO provides more specific clinical guidelines for patients with CKD and type 2 diabetes. For patients at CKD stage 3 or higher (eGFR ≥ 30 ml/min per 1.73 m^2), metformin is the recommended first-line treatment choice because of its safety, low cost, and potential cardiovascular benefits (KDIGO, 2020).

Sulfonylurea. The first-generation medications included chlorpropamide (no longer on the market), tolazamide (no longer on the market), tolbutamide (no longer on the market). Second-generation sulfonylureas include glyburide (approved 1998), glipizide (approved 1997) and glimepiride (approved 1995). Sulfonylurea treatment stimulates pancreatic insulin secretion. The most prominent side effects of the medication class are hypoglycemia and weight gain (ADA, 2018). Glyburide is metabolized in the liver, and is excreted by the kidneys and bile, approximately 50% by each route. Metabolites, that have hypoglycemic activity, can accumulate in CKD patients. And, therefore, glyburide is not recommended for CKD patients (ADA, 2018).

A retrospective cohort study by Roumie et al compared metformin monotherapy treatment with sulfonylureas in patients with new-onset type 2 diabetes (Roumie et al., 2019). Patients were followed up from the day of reaching a reduced kidney function threshold, defined as either an eGFR < 60 ml/min per 1.73 m^2 or serum creatinine level of

1.5 mg/dL for men or 1.4 mg/dL for women, and a total of 174,882 persistent met the criteria. The study showed that sulfonylureas versus metformin were associated with a higher risk of major adverse cardiovascular events: 1,394 events (29.2 per 1,000 person-years) among sulfonylurea users and 1048 events (23.0 per 1,000 person-years) among metformin users. The adjusted incident rate difference was 5.8 (95% CI, 4.1-7.3) fewer events per 1000-person years for metformin compared with sulfonylurea users. Cardiovascular events included hospitalization for acute myocardial infarction, stroke, transient ischemic attack, or cardiovascular death.

Other glucose-lowering medications

Alpha-glucosidase inhibitor class includes acarbose (approved 1995), and miglitol (approved 1996). These agents slow intestinal carbohydrate digestion and absorption (ADA, 2018).

Amylin analog class, currently includes one drug, pramlintide (approved 2005). It is a medication that patients inject subcutaneously before meals. The medication slows gastric emptying, increases the feeling of fullness, and suppresses postprandial glucagon secretion (ADA, 2018).

Bile acid sequestrant class, currently includes one drug, colesevelam (approved 2008), which has as its primary indication on treatment of hypercholesterolemia and improvement of glycemic control in type 2 diabetes. In the latter indication, colesvelam treatment reduces hepatic glucose production, increase incretin levels, and decrease glucose absorption (ADA, 2018).

Dopamine agonist class, bromocriptine (approved 2009) belongs to this class and is a dopamine receptor agonist. It may centrally regulate metabolism and increase insulin sensitivity (ADA, 2018).

Meglitinide class includes nateglinide (approved 2000) and repaglinide (approved 1997). Meglitinides stimulate pancreatic insulin secretion around mealtime (ADA, 2018).

Thiazolidinediones (TZD), members of the TZD class include pioglitazone (approved 2005) and rosiglitazone (approved 2002). These agents lower blood glucose by increasing insulin sensitivity in muscle and fat (ADA, 2018). TZDs have low risk of hypoglycemia and do not require dosing changes with varying degrees of kidney function. However, they can cause fluid retention and edema (Nesto et al., 2004). In September 2010, the FDA announced increased cardiovascular risks in patients treated with rosiglitazone (FDA, 2010). FDA removed the prescribing and dispensing restrictions for rosiglitazone in 2013 (FDA, 2013). In December 2016, the FDA announced that pioglitazone was associated with an increased risk of bladder cancer. (FDA, 2016)

Insulin therapy

Insulin regimens include long-acting (basal), intermediate-acting insulin, and mealtime insulin. Basal insulin options include glargine, glargine biosimilar, detemir, degludec. Neutral protamine hagedorn (NPH) is an intermediate-acting insulin, and typically injected twice daily. For meal-time insulin, options are short-acting analogs (human regular) and rapid-acting analogs (including lispro, aspart, glulisine and inhaled insulin). Insulin is a drug that undergoes metabolism and excretion in the kidneys. The kidneys normally dispose of 18% of the usual daily output of insulin. Reduction in

insulin dose may be needed in patients as kidney function declines. Clinical guidelines do not provide specific recommendations, and dosing adjustment is based on glucose control on an individual base (ADA, 2018). Meta-analysis studies have demonstrated lower risk of overall and nocturnal hypoglycemia for glargine or detemir compared with NPH insulin (Horvath et al., 2007; Owens et al., 2017). A randomized crossover study evaluated use of the short-acting insulin analog lispro in patients with impaired kidney function (serum creatinine <2.0 mg/dl and an albuminuria persistently ≥200 μg/min). Eleven patients, aged 59.3 years (range 42–72), completed the study. The study demonstrated improvement in glycemic control and safety compared with regular insulin (Ruggenenti et al., 2003).

Studies comparing newer glucose-lowering medications versus older glucose-lowering medications (sulfonylureas) related to hypoglycemia risk.

Results from two recent meta-analyses indicated lower risk of hypoglycemia in type 2 diabetes patients with SGLT2i versus sulfonylureas. One meta-analysis compared cardiovascular safety and efficacy of combination therapy with metformin-SGLT2i versus metformin-sulfonylureas in patients with type 2 diabetes (Gebrie et al., 2021). Nine trials were included in the analysis and involved 10,974 patients with type 2 diabetes. Patients taking metformin-SGLT2i versus metformin-sulfonylureas showed greater reduction in HbA1c (mean difference: − 0.10%, 95% CI [− 0.17, − 0.03], and significantly lower risk of hypoglycemia (relative risk: 0.13, 95% CI [0.10, 0.17], $p < 0.001$) (Gebrie et al., 2021). The second meta-analysis focused on comparing the efficacy and safety of SGLT2i with sulfonylureas as second-line therapy in patients with type 2 diabetes inadequately controlled on metformin (Chen et al., 2019). The analysis

included five trials involving 4,300 participants. Compared with sulfonylureas, SGLT2i led to no significant reduction in changes in HbA1c (mean difference: 0.06; 95% CI: [-0.12, 0.08]), but less hypoglycemia as an add-on to metformin (odds ratio: 0.12; 95% CI: 0.07-0.21) (Chen et al., 2019).

A meta-analysis specifically focused on type 2 diabetes patients with moderate to severe kidney impairment, and assessed the safety and efficacy of DPP-4i (Cheng et al., 2014). Among the studies included in the analysis, two clinical trials compared DPP-4i monotherapy with glipizide monotherapy. In the pooled analysis of these two clinical trials, DPP-4i versus glipizide monotherapy showed no difference in HbA1c lowering effect (−0.08%, 95% CI: −0.40 to 0.25) but DPP-4i had a lower incidence of hypoglycemia (rate ratio: 0.40, 95%CI: 0.23 to 0.69) (Cheng et al., 2014).

2.3 Literature review summary

Substantial evidence from clinical trials have shown significant kidney- or cardio-protective effects of SGLT2i and GLP-1RA in CKD patients with type 2 diabetes. Evidence supporting reduction of cardiovascular or kidney events were not seen with other glucose-lowering medications (e.g., TZD, sulfonylureas, insulin, and DPP-4i). Clinical trials showed safety and efficacy of DPP-4i in patients with type 2 diabetes and CKD, especially in CKD stages 4-5 patients and even in dialysis patients. We anticipate that percentages of CKD patients using these newer glucose-lowering agents (SGLT2i, GLP-1RA, and DPP-4i) will increase over time. Information on the trends in use of glucose-lowering medications in patients with CKD is limited. In addition, there is

limited data on the association of sociodemographic and clinical factors on the initiation of these newer glucose-lowering prescriptions in CKD patients.

Patients with CKD are likely to have higher risk for hypoglycemia. Risk of hypoglycemia was generally low in these large clinical trials of newer glucose-lowering medications (SGLT2i, GLP-1RA, and DPP4i). Results from meta-analyses of the clinical trials suggested that incidence of hypoglycemia may be lower with SGLT2i than sulfonylureas. However, information on safety issues of newer glucose-lowering medications from a real-world population perspective in CKD patients with type 2 diabetes is limited.

Chapter 3

Manuscript #1: Glucose-Lowering Medication Use in CKD: Analysis of US Medicare Beneficiaries between 2007 and 2016

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Abstract

Background: Information regarding utilization of glucose-lowering medications in patients with chronic kidney disease (CKD) is limited.

Study Design: Retrospective cohort study.

Setting & Participants: Medicare 5% random sample CKD patients with type 2 diabetes, 2007-2016.

Predictors: Study year, CKD stage, low-income subsidy (LIS) status, and demographic characteristics (age, sex, and race/ethnicity).

Outcomes: Trends in utilization of glucose-lowering medications.

Analytical Approach: Yearly cohorts of patients with CKD and type 2 diabetes were created. Descriptive statistics were used to report proportions of patients using glucose-lowering medications. To test overall trends in glucose-lowering medication classes, linear probability models with adjustment for age, sex, race/ethnicity, CKD stage, and LIS status were used.

Results: Metformin use increased significantly from 32.7% in 2007 to 48.7% in 2016. Use of newer classes of glucose-lowering medications increased significantly, including dipeptidyl peptidase 4 inhibitors (5.6%, 2007; 21.7%, 2016), glucagon-like peptide-1 receptor agonists (2.3%, 2007; 6.1%, 2016), and sodium-glucose cotransporter 2 inhibitors (0.2%, 2013; 3.3%, 2016). Newer insulin analog use increased from 37.2% in 2007 to 46.3% in 2013 and then remained steady. Use of sulfonylureas, thiazolidinediones, older insulins (human regular and neutral protamine hagedorn), alpha-glucosidase inhibitors, amylin mimetics, and meglitinides decreased significantly. Insulin

was the most highly used single medication class. Insulin use was higher among LIS than among non-LIS patients. Combination therapy was less common as CKD stage increased. *Limitations:* Patients with CKD and type 2 diabetes, and CKD stages, were identified with diagnosis codes, and could not be verified through medical record review. Our results may not be generalizable to younger CKD patients with type 2 diabetes. *Conclusions:* Use of metformin and newer glucose-lowering medication classes is increasing in CKD patients with type 2 diabetes. We anticipate that percentages of CKD patients using these newer agents will increase.

Introduction

Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD).[1] According to National Health and Nutrition Examination Survey data, prevalence of CKD (stages 3 and 4) among US adults with diagnosed diabetes was 24.5% (27.1% to 22.1%), and 4.9% (6.1% to 4.1%) among those without diabetes in 2011-2014.[2]

Besides lifestyle modifications and psychosocial care, diabetes treatment includes pharmacologic approaches for glycemic control. Selecting effective and safe glucose-lowering medications for CKD patients is challenging. Glucose-lowering medication pharmacokinetics can change, and some medications lose effectiveness as kidney function declines, necessitating dosage adjustments or discontinuation. Twelve classes of glucose-lowering medications are on the US market today (**Supplementary Table S3.1**): biguanides, sulfonylureas, thiazolidinediones (TZD), meglitinides/glinides, alpha-glucosidase inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, incretin mimetics/glucagon-like peptide-1 (GLP-1) receptor agonists, bile acid sequestrants, dopanmine-2 agonists, amylin mimetics, and insulins.[3] Evidence supporting their effectiveness in CKD patients is increasing. For example, Arjona Ferreira et al compared sitagliptin with glipizide regarding glucose lowering in patients with moderate-to-severe CKD and demonstrated efficacy of sitagliptin in a randomized clinical trial.[4] The EMPA-REG OUTCOME randomized controlled trial demonstrated lower rates of cardiovascular outcomes and kidney disease progression with empagliflozin than with placebo in patients with type 2 diabetes.[5,6]

Information on utilization of glucose-lowering medications in CKD patients is limited. Our study aimed to: 1) update trends in utilization of individual glucose-lowering medications and distinct therapeutic classes in CKD patients with diabetes, 2) determine which mono- and combination therapies were commonly prescribed for CKD patients with diabetes, and 3) examine patterns of glucose-lowering medication utilization in these patients by CKD stage.

Methods

Study population and data source

We evaluated an adult CKD population from the Medicare 5% random sample, provided by the United States Renal Data System.[7] We used 2007-2016 data, including patient enrollment and demographic characteristic information, and institutional Part A, non-institutional physician/supplier Part B, and prescription Part D claims files.

Study design and cohort construction

Yearly cohorts of patients with CKD and type 2 diabetes were created from January 1, 2007, to December 31, 2016. CKD and diabetes diagnoses were identified by International Classification of Disease, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) diagnosis codes.[8] Eligible patients had ≥ 1 code from inpatient services, home health, or skilled nursing facilities, or ≥ 2 codes from physician claims or outpatient services on different claim dates within each cohort year for CKD (**Supplementary Table S3.2)** and for type 2 diabetes (**Supplementary Table S3.3**). Use of two outpatient claims has been shown to increase sensitivity and specificity compared with using only one claim for diabetes.[9] Eligible patients who met the following criteria were included in

the study: 1) had CKD and type 2 diabetes, aged ≥ 18 years, and alive through each cohort year; 2) enrolled in Medicare Parts A, B, and D for the entire year, and not enrolled in a Medicare Advantage plan during any month; 3) did not develop ESKD during the year; and 4) received glucose-lowering medications.

CKD function definition

Kidney function was defined by CKD staging ICD-9/10-CM diagnosis codes (**Supplement Table S3.4)**. If multiple claims related to different CKD stages appeared in a cohort year, the most frequent stage (1 to 5) within the calendar year was used. If the same number of claims appeared for two or more stages, the highest severity stage was used. An unspecified stage code was used for patients without stage-specific codes.

Glucose-lowering medications

We used glucose-lowering medication names and classes provided in the American Diabetes Association (ADA) 2018 guideline, "Pharmacologic Approaches to Glycemic Treatment," to identify medications from Part D claims data.[3] Medication use was defined by at least one dispensed, Part D-covered medication during the calendar year. Use of these agents individually and within each therapeutic class was reported. We also reported on monotherapy for each glucose-lowering medication class. To identify combination use of multiple glucose-lowering medication classes, information on days' supply was used. Use of more than one glucose-lowering medication class overlapping for at least two continuous months was defined as combination therapy.

Statistical analysis

We used descriptive statistics to report proportions of individuals using any glucose-lowering medication or class by calendar year. To test overall trends in glucose-lowering medication classes, linear probability regression models with adjustment for age, sex, race/ethnicity, CKD stage, and low-income subsidy (LIS) status were used. To account for repeated observations (calendar years) per patient, generalized estimating equations (GEE) were used to fit the model. For 2016, we report more detailed information on proportions of patients receiving monotherapy or combination therapy by CKD stage. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

The University of Minnesota Institutional Review Board approved the study (IRB ID: STUDY00000991). Participants' informed consent was not required.

Results

Final sample sizes of patients meeting inclusion criteria and using glucose-lowering medications ranged from 19,257 in 2007 to 52,626 in 2016. In 2016, 21% of CKD and type 2 diabetes patients had no prescriptions for glucose-lowering medications. A consort diagram for 2016 patients is provided in **Figure 3.1**. In 2016, 86.3% were aged ≥ 65 years. Distributions of age and race/ethnicity were similar across yearly cohorts (**Table 3.1**). The proportion of patients at stage 3 CKD in 2016 (50.5%) was higher than in 2007 (28.5%) or 2012 (45.4%). The proportion of patients with LIS status in 2016 was lower than in 2007 or 2012 (**Table 3.1**).

Trends in utilization of glucose-lowering medication classes

Several glucose-lowering medication classes showed statistically significant increase in use trends from 2007-2016, including metformin, DPP-4 inhibitors, GLP-1receptor agonists, SGLT2 inhibitors, and newer insulin analogs (**Figure 3.2**, **Supplementary Table S3.5)**. Metformin use increased from 32.7% in 2007 to 48.7% in 2016. Use of newer classes of glucose-lowering medication increased sharply, including DPP-4 inhibitors (5.6% in 2007, 21.7% in 2016), GLP-1 receptor agonists (2.3% in 2007, 6.1% in 2016), and SGLT2 inhibitors (0.2% in 2013, 3.3% in 2016). Use of newer insulin analogs (aspart, lispro, glulisine, detemir, glargine, degludec) increased from 37.2% in 2007 to 46.3% in 2013 and then remained steady. Use of sulfonylureas, TZDs, older insulins, alpha-glucosidase inhibitors, amylin mimetics, and meglitinides decreased significantly. Sulfonylurea use declined from 50.1% in 2007 to 37.9% in 2016 and TZD use from 32.2% in 2007 to 7.0% in 2016. Use of older insulins (human regular and neutral protamine hagedorn [NPH]) declined from 26.4% in 2007 to 7.1% in 2016. Trends in all glucose-lowering medication classes are shown in **Figure 3.2**. We also examined trends in glucose-lowering medication classes by age (< 65, ≥ 65 years). Patients aged younger than 65 years were mainly people with disabilities. Trends were similar between these age groups. However, use of sulfonylureas, newer insulin analog insulins, or older insulins (28.6%, 59.9%, 10.1% in 2016, respectively) among patients aged younger than 65 years differed from use among patients aged 65 years or older (39.3%, 41.5%, 6.6% in 2016, respectively) (data not shown).

Trends in use of specific glucose-lowering medications

Sitagliptin was the most commonly prescribed DPP-4 inhibitor; use increased from 5.6% in 2007 to 15.0% in 2016 (**Figure 3.3A)**. Use of linagliptin (approved in

2011) increased from 0.1% in 2011 to 6.0% in 2016. Compared with other GLP-1 receptor agonists, use of liraglutide (approved in 2010) increased more (0.3% in 2010 to 3.6% in 2016), and use was higher in 2016. Use of SGLT2 inhibitors (canagliflozin, empagliflozin, or dapagliflozin) remained very low in 2016, but was increasing. For example, use of canagliflozin (approved in 2013) increased from 0.2% in 2013 to 2.4% in 2016. Except for glimepiride, which showed an increasing trend from 13.2% in 2007 to 16.2% in 2016, use of other sulfonylureas decreased (e.g., glyburide use decreased from 16.5% to 2.2% from 2007 to 2016) (**Figure 3.3B**). A large decline in use of TZDs occurred from 2007 to 2016; rosiglitazone was essentially unused by 2012.

Use of newer analog insulin therapy increased, especially insulin detemir (2.4% in 2007, 11.7% in 2016), while NPH insulin use declined from 18.9% in 2007 to 4.8% in 2016, and regular insulin from 21.9% in 2007 to 5.6% in 2016 (**Figure 3.3C**).

Use of glucose-lowering medication classes by CKD stage

In 2016, percentages of CKD patients with type 2 diabetes receiving insulin increased as CKD stage increased: 41% at stages 1-2, 66% at stages 4-5. Metformin use decreased as CKD stage increased: 63% at stages 1-2, 15% at stages 4-5. Use of DPP-4 inhibitors and GLP-1 receptor agonists was similar across CKD stages (**Figure 3.4)**. Single and dual combination use of glucose-lowering medications was 49.6% and 39.9% among CKD patients in 2016, respectively (**Supplementary Figure S3.1)**. The proportion of patients using two or more glucose-lowering medication classes decreased as CKD stage increased. Triple combination therapy was used in 16% and 9% of CKD stages 1-2 and 4-5 patients, respectively; quadruple combination therapy was uncommon: 4% at stages 1-2, 1% at stages 4-5 (**Figure 3.5)**.

Among CKD patients with diabetes who received a single glucose-lowering medication class in 2016, the most highly used class was insulin (41%) (**Table 3.2**). The most highly used dual combination therapies in 2016 were metformin and sulfonylureas (20.1%) and metformin and insulin (14.5%). The most highly used triple combination therapies were metformin, sulfonylureas, and DPP-4 inhibitors (5.4%) and metformin, sulfonylureas, and insulin (5.2%) (**Table 3.3**).

Discussion

We present utilization patterns of glucose-lowering medications among CKD patients, based on Medicare data. Use of metformin and newer glucose-lowering medication classes (DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors) showed statistically significant upward trends during the study timeframe. Insulin was the most highly used single class, with long-acting detemir use increasing the most. Combination therapy was less common as CKD stage increased.

Two recent analyses of glucose-lowering medication class use in the general population are available. Sumarsono et al published trends in and expenditures of glucose-lowering medications among US Medicare beneficiaries, 2012-2017.[10] Metformin use increased over the study timeframe and was the most commonly prescribed glucose-lowering medication, while amylin analogues were the least commonly prescribed class.[10] Using Medical Expenditure Panel Survey data (MEPS) from 2008 to 2015, Raval et al examined trends in glucose-lowering medication use among US individuals with diabetes, and showed similar results.[11] Use of metformin increased from 47.8% in 2008 to 59.0% in 2015; use of TZDs and sulfonylureas

decreased; use of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors increased.[11] We show utilization patterns of glucose-lowering medication classes among CKD patients similar to those in the general population, except that insulin was the most commonly used glucose-lowering medication class in CKD patients, versus metformin in the general population. We noted a greater increase in DPP-4 inhibitor use among CKD patients (8.4% to 21.5%) from 2008 to 2015, compared with the general population (6.2% to 12.4%) in the MEPS study. Regarding multiclass therapy use in the general population, the MEPS study reported that in 2015 the two most common dual combination therapies were metformin and sulfonylureas and metformin and insulin; the two most common triple combination therapies were metformin, sulfonylureas, and DPP-4 inhibitors and metformin, sulfonylureas, and insulin.[11] We observed the same common patterns of combination therapies in CKD patients in 2016.

We observed an increase in metformin use in CKD patients. In 2016, 63%, 41%, and 65% of patients at CKD stages 1-2, stage 3, and unspecified stage with diabetes, respectively, used metformin. Metformin is inexpensive and effectively lowers plasma glucose.[3] The United Kingdom Prospective Diabetes Study demonstrated a reduced risk of cardiovascular events and death with metformin compared with sulfonylureas, insulin, or diet restriction among overweight type 2 diabetes patients.[12] However, metformin is mainly eliminated by the kidneys and is associated with risk of lactic acidosis, which has in the past limited its use in patients with CKD. In recent years, several observational studies have shown that metformin can be safely used in patients with mild to moderate kidney function.[13–15] In 2016, the US Food and Drug Administration (FDA) requested a labeling change regarding metformin use in patients with reduced kidney function.[16]

Accordingly, the ADA and European Association for the Study of Diabetes 2019 guidelines recommend that metformin be considered as the first-line treatment for patients with type 2 diabetes with estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73 m^2.[17] Consistent with the FDA label change, ADA guidelines state that metformin is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2.[3,18,19] Out results showed 15% metformin use in 2016 among CKD stages 4-5 patients; further investigation into effectiveness and safety of metformin therapy in severe CKD is warranted.

We found a rapid increase in use of several new therapeutic classes, including DPP-4 inhibitors (first approval, 2006, sitagliptin), GLP-1 receptor agonists (2005, exenatide), and SGLT2 inhibitors (2013, canagliflozin). Much higher DPP-4 inhibitor use (21.7%) than GLP-1 receptor agonist (6.1%) or SGLT2 inhibitor (3.3%) use in 2016 was unsurprising, due to their being on the market longer. DPP-4 inhibitor use was even higher (24%) among CKD stages 4-5 patients, driven by sitagliptin use. This trend was most likely due to clinician comfort with sitagliptin, given pharmacokinetic and safety studies in CKD patients showing that a reduced dose was effective and safe even in patients receiving hemodialysis.[20] We showed that sitagliptin use increased from 5.6% in 2007 to 15.6% in 2013, then remained relatively constant. Linagliptin use also increased from 0.1% in 2011 to 6% in 2016. Linagliptin is eliminated predominantly via the bile, and hence does not require dose adjustment for CKD patients.[21] In contrast, all other drugs in this class (sitagliptin, saxagliptin, alogliptin) are excreted mainly by the kidneys; ADA guidelines recommend dose adjustments in CKD patients.[3,18]

The SGLT2 inhibitor class is the newest class of oral glucose-lowering medications. In March 2008, the FDA issued new guidance on evaluation of cardiovascular risk during development of new glucose-lowering medications.[22] Following the FDA guidance, recent glucose-lowering medication clinical trials include cardiovascular and kidney-related outcomes. The EMPA-REG OUTCOME clinical trial demonstrated lower rates of cardiovascular events and lower risk of incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of kidney-replacement therapy, or death from kidney disease) for empagliflozin than for placebo in patients with type 2 diabetes at high risk for cardiovascular events.[5,6,23] Recently, the CANVAS trial showed that canagliflozin reduced rates of the cardiovascular composite outcome, albuminuria progression, and kidney composite outcome compared with placebo among 10,142 patients with type 2 diabetes and high cardiovascular risk.[24] The DECLARE-TIMI 58 trial evaluated cardiovascular safety of dapagliflozin in patients with type 2 diabetes and cardiovascular risk.[25] Compared with other SGLT2 inhibitor trials in which the primary outcome was cardiovascular events, the CREDENCE trial was designed to assess the effects of canagliflozin primarily on kidney outcomes in patients with type 2 diabetes and albuminuric CKD.[26] Because the CREDENCE trial evaluated patients with baseline eGFR down to 30 mL/min/1.73 m^2, the label recommends use down to that level. Empagliflozin and dapagliflozin trials did not include patients with eGFR < 45 mL/min/1.73 m^2, and labels suggest avoiding use if eGFR below that level. We anticipate that percentages of CKD patients using these agents will greatly increase above the 2016 level, considering positive trial results.

Most current GLP-1 receptor agonists are injectable. The first oral GLP-1 receptor agonist, semaglutide, was approved in 2019 by the FDA.[27] Our data showed that liraglutide and dulaglutide use gradually increased since approval in 2010 and 2014, respectively. LEADER clinical trial results showed a significant benefit with liraglutide compared with placebo on cardiovascular events and composite kidney outcomes of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, ESKD, or death due to kidney disease.[28,29] The AWARD-7 clinical trial assessed the efficacy and safety of dulaglutide among patients with type 2 diabetes and CKD stages 3-4. Compared with insulin glargine, efficacy of dulaglutide was similar in glycemia control, with a lower rate of hypoglycemia, a smaller decline in eGFR, and a greater reduction in albuminuria.[30] Use of these agents will likely increase in CKD patients, considering data from these recent trials.

We observed a significant decrease in TZD use from 2008 to 2016, initially due to study reports and safety warnings issued by the FDA with rosiglitazone. In September 2010, the FDA announced increased cardiovascular risks in patients treated with rosiglitazone.[31] Despite FDA action that removed the prescribing and dispensing restrictions for rosiglitazone in 2013 based on new data,[32] rosiglitazone use remained almost non-existent. In December 2016, the FDA announced that pioglitazone was associated with an increased risk of bladder cancer,[33] but use has remained steady at 7.5% since 2013.

We observed that sulfonylurea use significantly decreased from 2007 to 2016. Specifically, glyburide use decreased from 16.5% in 2007 to 2.2% in 2016. However, glimepiride use consistently increased from 13.2% in 2007 to 16.2% in 2016, and

glipizide use was relatively constant at approximately 21%. The second-generation agents (glyburide, glipizide, glimepiride) have largely replaced first generation drugs (chlorpropamide, tolazamide, tolbutamide) in the general population, due to lower risk of hypoglycemia. Glyburide is metabolized in the liver, and is excreted by the kidneys and bile, approximately 50% by each route. Some metabolites, which have hypoglycemic activity, can accumulate in CKD patients.[34] Glyburide is not recommended for CKD patients.[3] An observational study by Roumie et al compared metformin monotherapy treatment with sulfonyureas in patients with diabetes and reduced kidney function (eGFR < 60 mL/min/1.73 m^2), and showed that sulfonylureas were associated with a higher risk of major adverse cardiovascular events.[35] ADA 2019 guidelines recommend metformin as the preferred first-line diabetes treatment in CKD patients, depending on eGFR, and the best noninsulin added treatment to initial therapy is a SGLT-2 inhibitor or GLP-1 receptor agonist due to their cardiovascular and kidney-related benefits.[19]

Utilization patterns of insulin in CKD patients in our findings were similar to those in the general population.[10] Use of newer insulin analogs significantly increased and surpassed use of older insulins (human regular or NPH) between 2007 and 2016. In addition, we observed that the percentage of glargine use was higher (28% in 2016) than other insulins, and detemir and lispro use continued to rise. Meta-analysis studies demonstrated lower risk of overall and nocturnal hypoglycemia for glargine or detemir compared with NPH insulin.[36,37] A randomized crossover study evaluated use of the short-acting insulin analog lispro in patients with impaired kidney function, and demonstrated improvement in glycemic control and safety compared with regular insulin.[38] We also noted that insulin use in LIS patients was higher than in non-LIS

patients (**Supplementary Figure S3.2**). High out-of-pocket costs that non-LIS patients experience likely affect medication choice. The Medicare Part D program offers LIS benefits to enrollees with limited assets and income. The LIS provides full or partial waivers for out-of-pocket cost-sharing requirements including premiums, deductibles, and copayments.

Our findings reflect updated ADA guidelines and results of clinical trials. Kidney Disease: Improving Global Outcomes (KDIGO) provides more specific clinical guidelines for patients with CKD and type 2 diabetes. For patients at CKD stage 4 or higher (eGFR $\geq$ 30 mL/min/1.73 m^2), metformin is the recommended first-line treatment choice because of its safety, low cost, and potential cardiovascular benefits. A SGLT-2 inhibitor is recommended in the glucose-lowering treatment regimen. In patients who have not achieved individualized glycemic targets despite use of metformin and a SGLT-2 inhibitor, or who are unable to use those medications, a GLP-1 receptor agonist is recommended.[39]

Distribution of CKD stage varied across our yearly cohorts. CKD stage-specific diagnosis codes (585.X) were first introduced in 2006, and have been used increasingly. In 2007, CKD stage-specific codes accounted for only 49% of all CKD diagnosis codes, but for 68% in 2015.[40] We conducted trends analysis of glucose-lowering medication classes with adjustment for CKD stage.

Our study has several strengths. We provide a comprehensive picture and contemporary trends in utilization patterns of glucose-lowering medications in older adults with CKD and type 2 diabetes enrolled in Medicare Part D. We use actual medication claims dispensing records rather than other data sources that might measure

prescribing patterns. This is the first evaluation of use of combination therapy and glucose-lowering medications by CKD stage.

Our analysis also has several limitations. Clinical characteristics were measured based on administrative claims. In our study, patients with CKD and type 2 diabetes, and CKD stages, were identified with diagnosis codes, and could not be verified through medical record review or laboratory values. Second, information provided in Part D claims is based on prescription claims. How patients take these prescriptions is unknown. Last, our analysis cohort consisted of CKD patients enrolled in Medicare Part D; utilization patterns may differ for patients enrolled in non-Part D prescription plans or Medicare Advantage plans or other types of health insurance. The Medicare data set does not include patients aged younger than 65 years, except people with disabilities, and we excluded ESKD patients.

Conclusion

Our study results can help providers understand current utilization patterns of glucose-lowering medications in CKD patients. Further investigations are needed to examine the impact of newly published clinical trial results on utilization patterns of glucose-lowering medications in CKD patients and assess healthcare outcomes related to safety and effectiveness of glucose-lowering medications in CKD using real world data.

Article Information Section

Authors' Contributions

Research idea and study design: JZ, AC, WSP; data acquisition: JZ, WSP; data analysis/interpretation: JZ, EW, WSP; statistical analysis: JZ, EW, WSP; supervision or mentorship: WSP. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 3.1. Characteristics of CKD patients aged ≥ 18 years with type 2 diabetes using glucose-lowering medication, Medicare 5% CKD claims, in 2007, 2012, and 2016

	2007		2012		2016	
	n	Percent	*n*	Percent	*n*	Percent
Total	19,257		31,888		52,626	
Age, years	73.0±11.0		73.9±10.7		73.7±10.2	
Age category, years						
18-44	336	1.7	441	1.4	576	1.1
45-64	3,014	15.7	4,407	13.8	6,612	12.6
65-74	6,757	35.1	10,960	34.4	20,378	38.7
75-84	6,618	34.4	11,121	34.9	17,716	33.7
≥ 85	2,532	13.2	4,959	15.6	7,344	14.0
Sex						
Male	7,992	41.5	14,243	44.7	25,744	48.9
Female	11,265	58.5	17,645	55.3	26,882	51.1
Race/ethnicity						
White	14,044	72.9	23,443	73.5	40,148	76.3
Black	3,376	17.5	5,217	16.4	7,516	14.3
Native American	162	0.8	217	0.7	333	0.6
Asian	534	2.8	1,072	3.4	1,521	2.9
Hispanic	832	4.3	1,296	4.1	1,679	3.2
Other	290	1.5	565	1.8	956	1.8
Unknown	19	0.1	78	0.2	473	0.9
LIS status						
Non-LIS	7,891	41.0	14,756	46.3	31,101	59.1
LIS	11,366	59.0	17,132	53.7	21,525	40.9
CKD stage						
1	497	2.6	686	2.2	995	1.9
2	1,111	5.8	2,197	6.9	4,343	8.3

3	5,484	28.5	14,483	45.4	26,593	50.5
4	1,857	9.6	3,005	9.4	3,815	7.2
5	160	0.8	160	0.5	193	0.4
Unk./unspc.	10,148	52.7	11,357	35.6	16,687	31.7

CKD, chronic kidney disease; LIS, low-income subsidy; Unk/unspc, CKD stage unknown or unspecified.

Note: values for age as a continuous variable are given as mean ± standard deviation.

Table 3.2. Use of glucose-lowering medication classes among CKD patients with type 2 diabetes using monotherapy, in 2016

Class	*n*	Percent
Insulins	10,687	41.0
Metformin	8,303	31.8
Sulfonylureas	4,602	17.6
DPP-4 inhibitors	1,519	5.8
Thiazolidinediones	418	1.6
Meglitinides	233	0.9
GLP-1 receptor agonists	179	0.7
Bile acid sequestrants	68	0.3
SGLT2 inhibitors	50	0.2
Alpha-glucosidase inhibitors	17	0.1
Amylin mimetics	*	*
Dopamine-2 agonists	*	*

CKD, chronic kidney disease; DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors.

Note: * refers to counts of 10 or fewer patients. Number of CKD patients with type 2 diabetes using monotherapy = 26,081.

Table 3.3. Use of common glucose-lowering medication classes combination therapy among CKD patients with type 2 diabetes using more than one glucose-lowering medication class, in 2016

Combination Therapy	*n*	Percent
Metformin + sulfonylurea	5,343	20.1
Metformin + insulin	3,859	14.5
Sulfonylurea + insulin	2,728	10.3
Metformin + DPP-4	2,060	7.8
Sulfonylurea + DPP-4	1,801	6.8
DPP-4 + insulin	1,710	6.4
Metformin + sulfonylurea + DPP-4	1,432	5.4
Metformin + sulfonylurea + insulin	1,368	5.2
GLP-1 + insulin	818	3.1

CKD, chronic kidney disease; DPP4, dipeptidyl peptidase-4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists;

Note: Utilization of combination therapy ≥ 3% shown in the Table 3. Number of CKD patients with type 2 diabetes using more than one glucose-lowering medication class = 26,545.

Figure Legends

Figure 3.1. Consort diagram for patient selection in 2016. CKD, chronic kidney disease; ESKD, end stage kidney disease.

Figure 3.2. Trends in utilization of glucose-lowering medication classes among chronic kidney disease patients with type 2 diabetes between 2007 and 2016. DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors. *Note:* Newer insulin analogs include aspart, lispro, glulisine, detemir, glargine, degludec. Older insulins include human regular and neutral protamine hagedorn (NPH).

Figure 3.3. Trends in utilization of specific glucose-lowering medications among chronic kidney disease patients with type 2 diabetes between 2007 and 2016. Panel A, trends in DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors use. Panel B, trends in metformin, sulfonylureas (second generation), and thiazolidinediones use. Panel C, trends in insulins use. DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; insulin nph, insulin neutral protamine hagedorn; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors.

Figure 3.4. Percent using glucose-lowering medication classes among chronic kidney disease patients with type 2 diabetes by chronic kidney disease stage in 2016.
Abbreviation: DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors; stage u, chronic kidney disease stage unknown or unspecified.

Figure 3.5. Percent using monotherapy and combination therapy among chronic kidney disease patients with type 2 diabetes by chronic kidney disease stage in 2016.

Abbreviation: stage u, chronic kidney disease stage unknown or unspecified.

Figure 3.1.

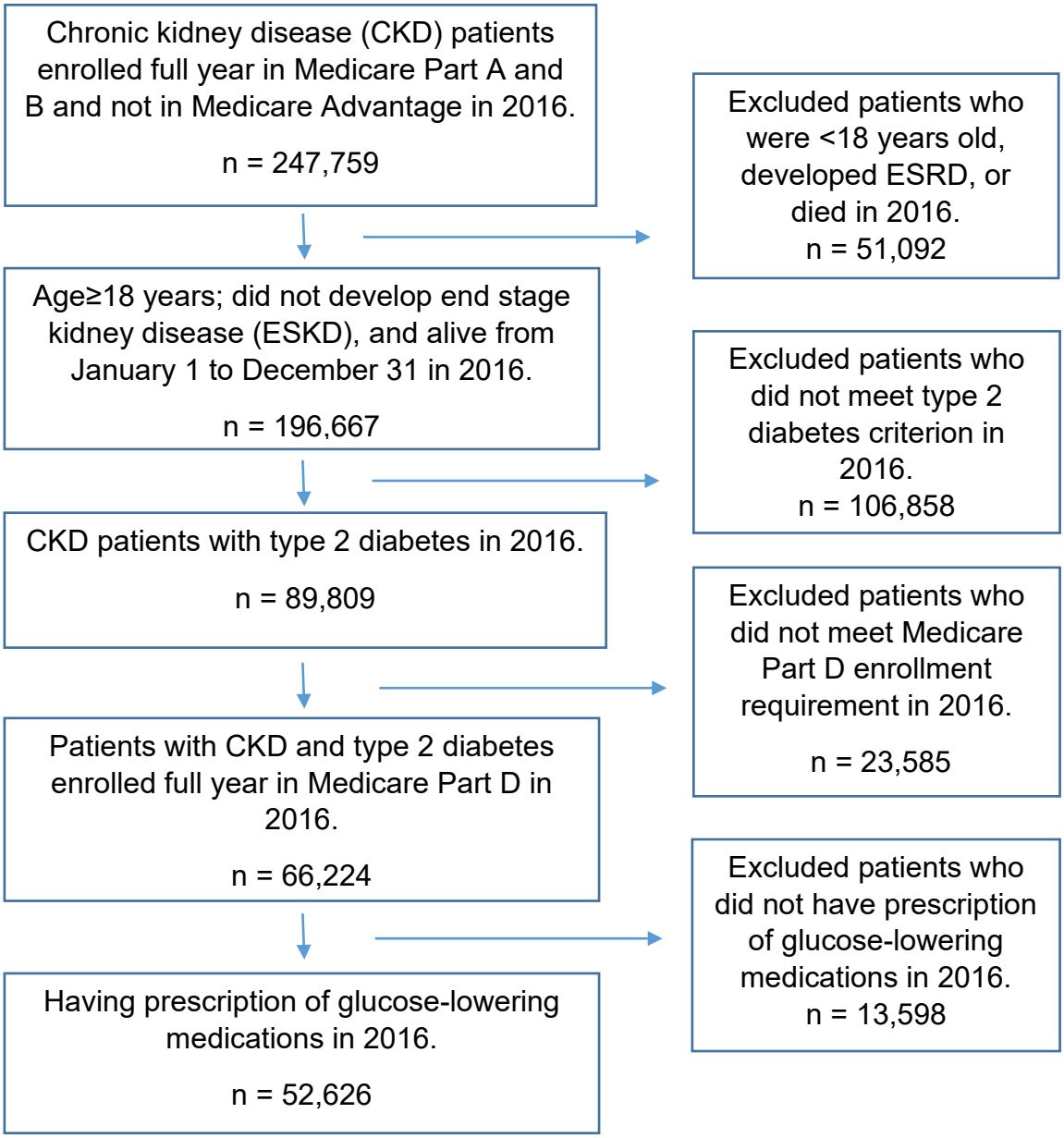

Chronic kidney disease (CKD) patients enrolled full year in Medicare Part A and B and not in Medicare Advantage in 2016.
n = 247,759
Excluded patients who were <18 years old, developed ESRD, or died in 2016.
n = 51,092
Age≥18 years; did not develop end stage kidney disease (ESKD), and alive from January 1 to December 31 in 2016.
n = 196,667
Excluded patients who did not meet type 2 diabetes criterion in 2016.
n = 106,858
CKD patients with type 2 diabetes in 2016.
n = 89,809
Excluded patients who did not meet Medicare Part D enrollment requirement in 2016.
n = 23,585
Patients with CKD and type 2 diabetes enrolled full year in Medicare Part D in 2016.
n = 66,224
Excluded patients who did not have prescription of glucose-lowering medications in 2016.
n = 13,598
Having prescription of glucose-lowering medications in 2016.
n = 52,626

Figure 3.2.

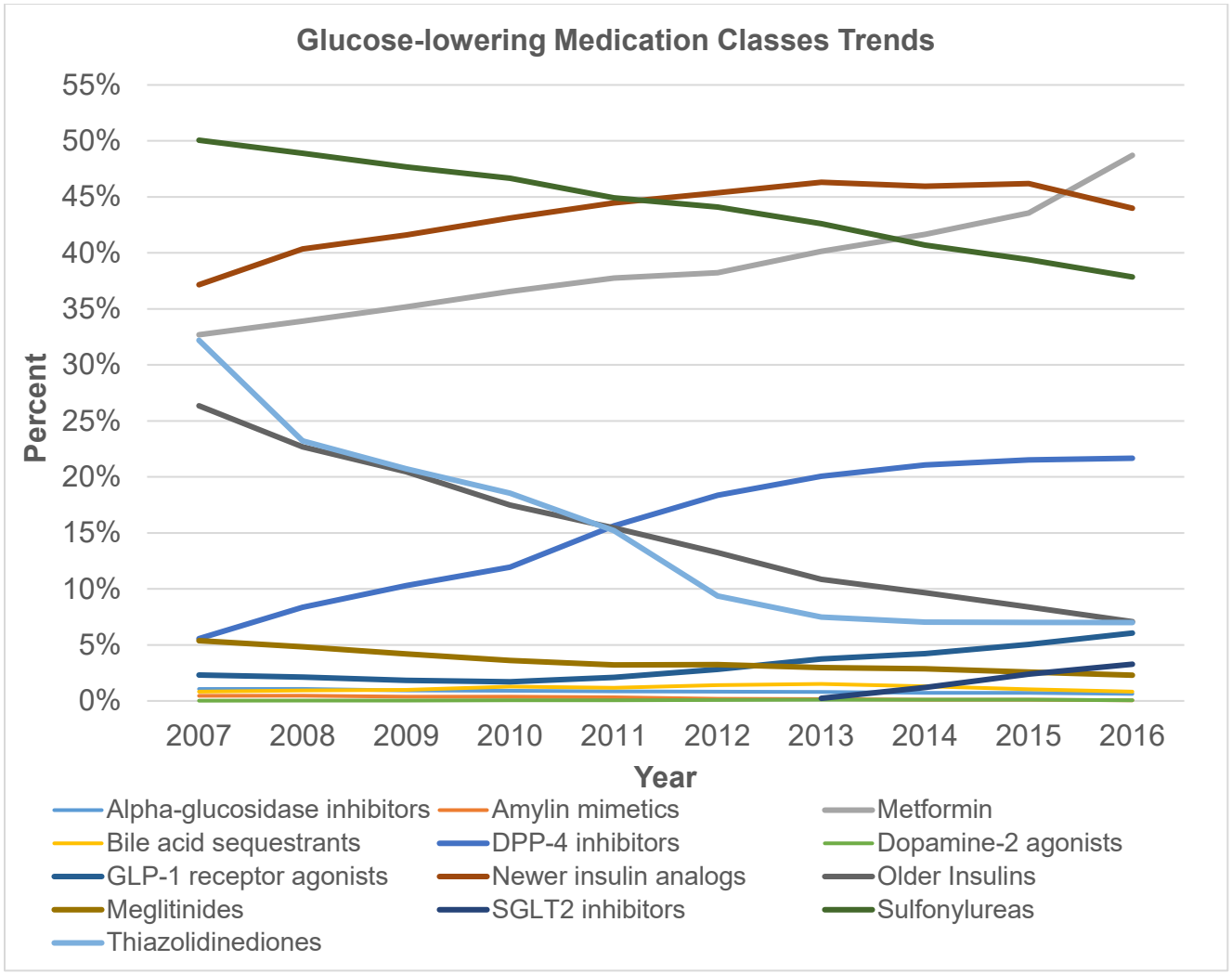

Glucose-lowering Medication Classes Trends
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percent
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year
Alpha-glucosidase inhibitors
Amylin mimetics
Metformin
Bile acid sequestrants
DPP-4 inhibitors
Dopamine-2 agonists
GLP-1 receptor agonists
Newer insulin analogs
Older Insulins
Meglitinides
SGLT2 inhibitors
Sulfonylureas
Thiazolidinediones

Figure 3.3A.

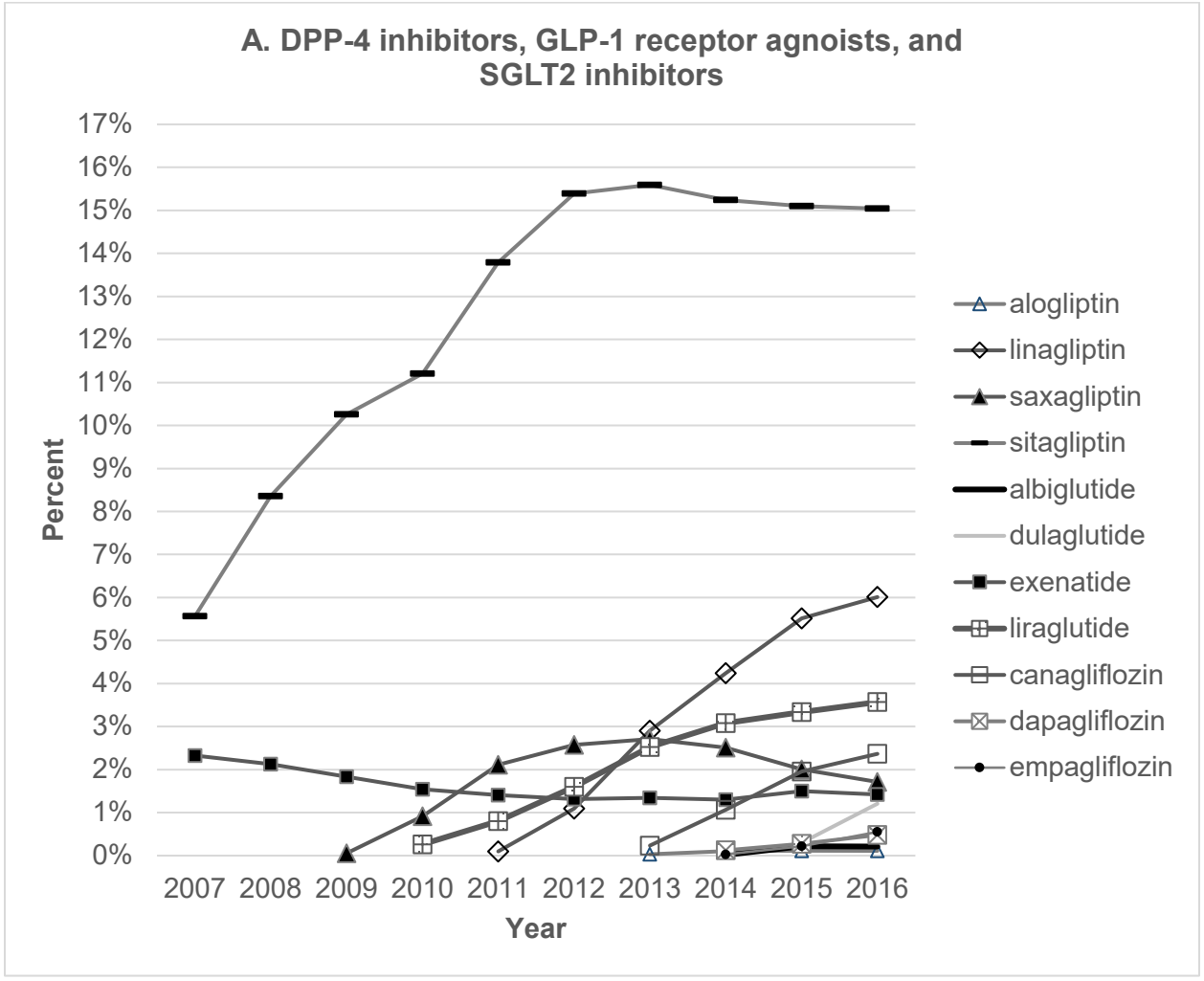

A. DPP-4 inhibitors, GLP-1 receptor agnoists, and SGLT2 inhibitors
Percent
17%
16%
15%
14%
13%
12%
11%
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year
alogliptin
linagliptin
saxagliptin
sitagliptin
albiglutide
dulaglutide
exenatide
liraglutide
canagliflozin
dapagliflozin
empagliflozin

Figure 3.3B.

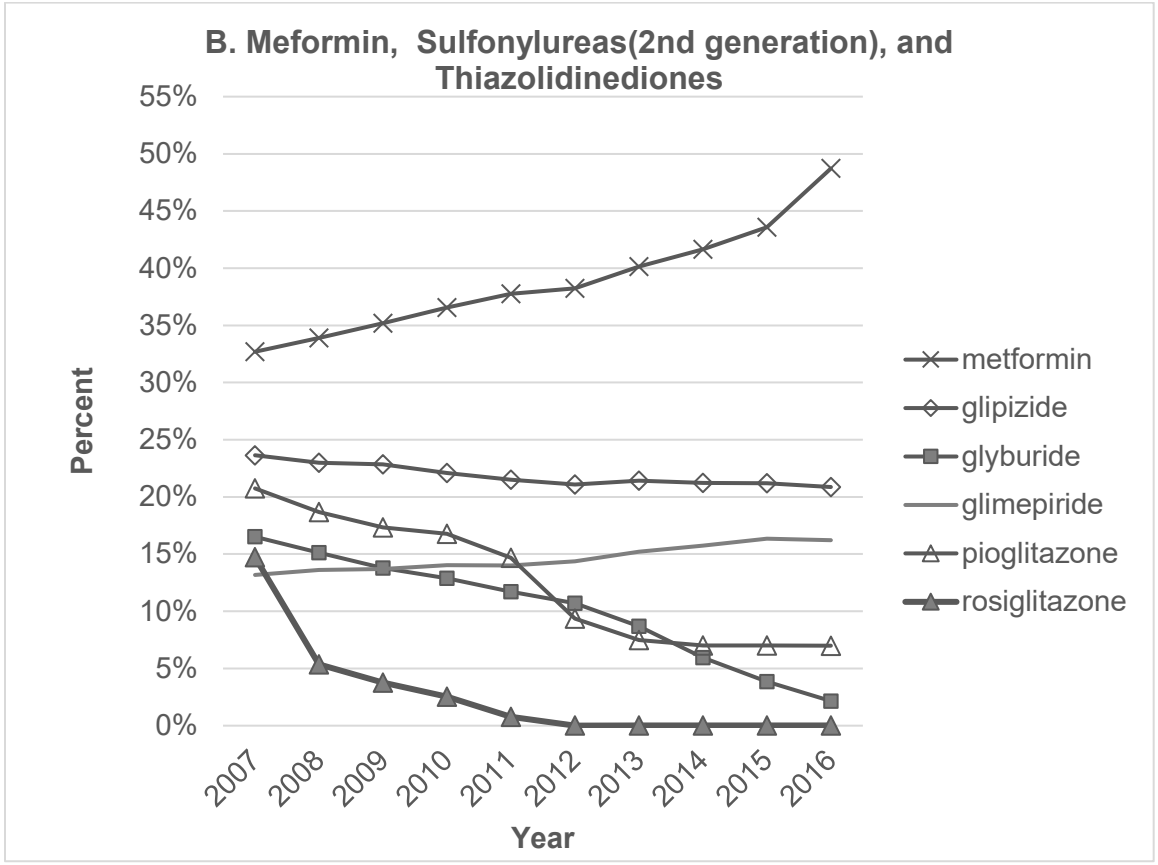

B. Meformin, Sulfonylureas(2nd generation), and Thiazolidinediones
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percent
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year
metformin
glipizide
glyburide
glimepiride
pioglitazone
rosiglitazone

Figure 3.3C.

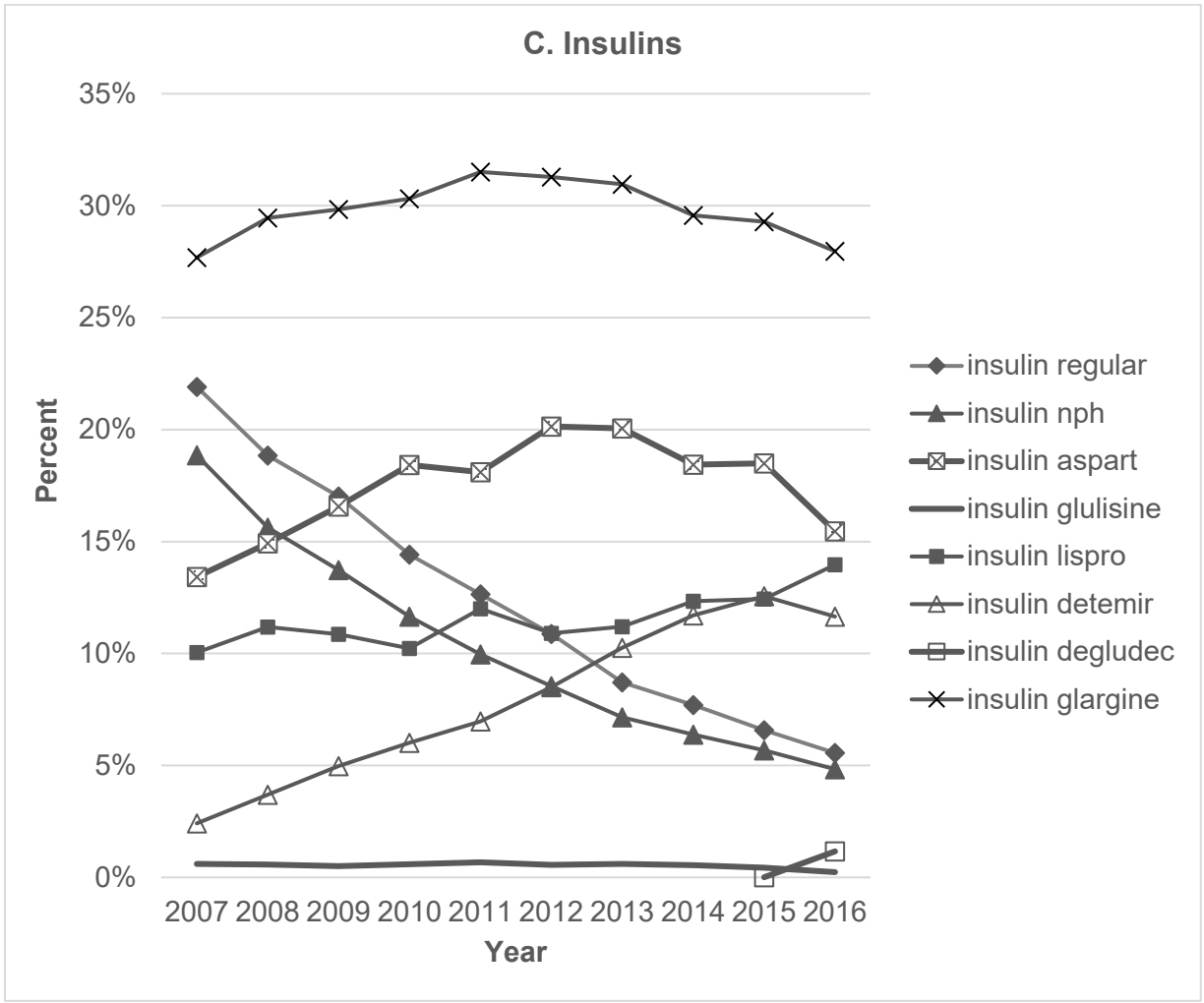

C. Insulins
35%
30%
25%
20%
15%
10%
5%
0%
Percent
2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
Year
insulin regular
insulin nph
insulin aspart
insulin glulisine
insulin lispro
insulin detemir
insulin degludec
insulin glargine

Figure 3.4.

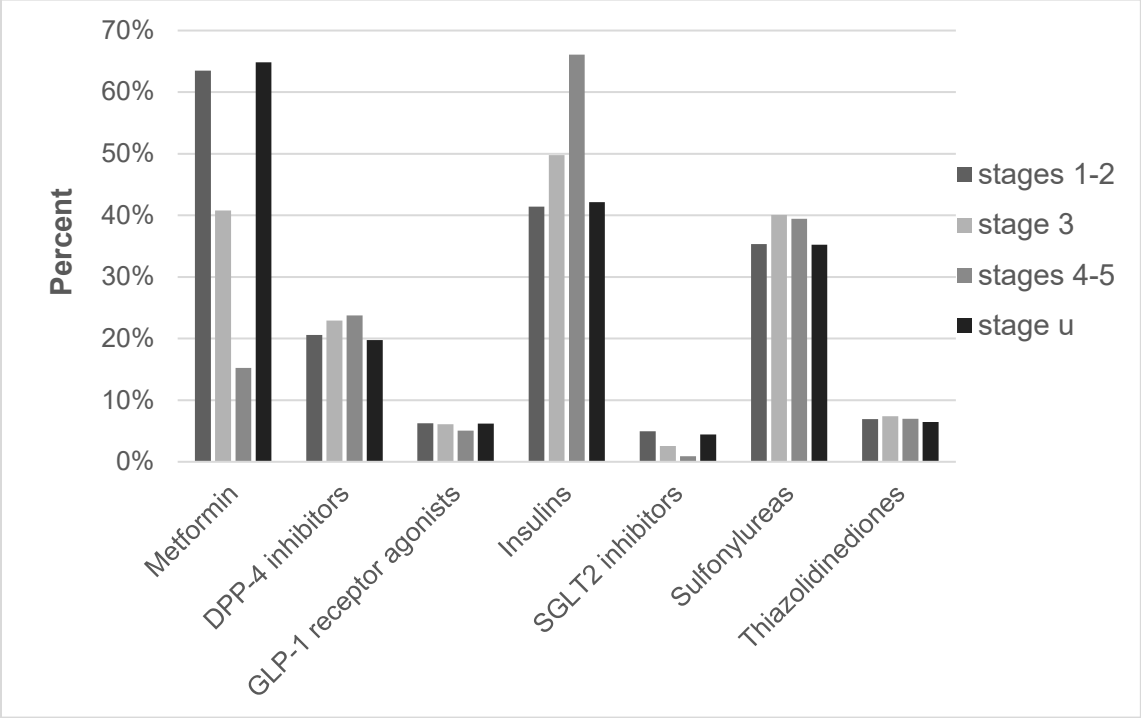
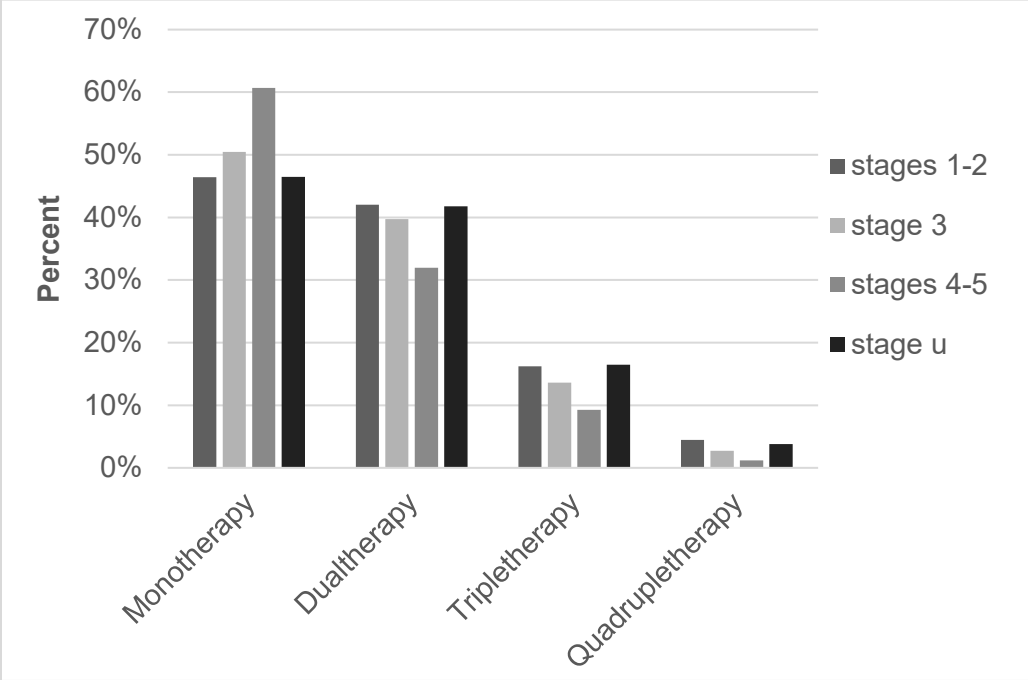

70%
60%
50%
40%
30%
20%
10%
0%
Percent
stages 1-2
stage 3
stages 4-5
stage u
Metformin
DPP-4 inhibitors
GLP-1 receptor agonists
Insulins
SGLT2 inhibitors
Sulfonylureas
Thiazolidinediones

Figure 3.5.


70%
60%
50%
40%
30%
20%
10%
0%
Percent
stages 1-2
stage 3
stages 4-5
stage u
Monotherapy
Dualtherapy
Tripletherapy
Quadruplethera py

Supplementary Material

Supplementary Table S3.1. Glucose-lowering medication classes and medications

Glucose-Lowering Medication Class	Medication
Biguanides	Metformin
Sulfonylureas	
First generation	Chlorpropamide
	Tolazamide
	Tolbutamide
Second generation	Glyburide
	Glipizide
	Glimepiride
Meglitinides (glinides)	Repaglinide
	Nateglinide
Thiazolidinediones	Pioglitazone
	Rosiglitazone
Alpha-glucosidase inhibitors	Acarbose
	Miglito
Dipeptidyl peptidase-4 inhibitors	Sitagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
Bile acid sequestrants	Colesevelam
Dopamine-2 agonists	Bromocriptine
Sodium glucose cotransporter-2 inhibitors	Canagliflozin
	Dapagliflozin
	Empagliflozin
Glucagon-like peptide-1 receptor agonists	Exenatide
	Exenatide extended release
	Liraglutide
	Albiglutide
	Lixisenatide
	Dulaglutide
Amylin mimetics	Pramlintide
Insulins	Rapid-acting analogs
	- Lispro
	- Aspart
	- Glulisine
	Short-acting
	- Human Regular
	Intermediate-acting
	- Human NPH
	Basal insulin analogs
	- Glargine
	- Detemir
	- Degludec

NPH, neutral protamine hagedorn.

Source: American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2018.

Supplementary Table S3.2. ICD-9/10-CM diagnosis codes for chronic kidney disease

ICD-9-CM	016.0; 095.4; 189.0,189.9; 223.0; 236.91; 250.4; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 447.3; 572.4; 581-583; 585- 588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4
ICD-10-CM	A18.11, A52.75, B52.0, C64.x, C68.9, D30.0x, D41.0x-D41.2x, D59.3, E08.2x, E09.2x, E10.2x, E10.65, E11.2x, E13.2x, E74.8, I12.xx, I13.0, I13.1x, I13.2, K76.7, M10.3x, M32.14, M32.15, N01.x-N08.x, N13.1, N13.1x-N13.39, N14.x,N15.0, N15.8, N15.9, N16, N18.1-N18.5, N18.8, N18.9, N19, N25.xx, N26.1, N26.9, O10.4xx, O12.xx, O26.83x, O90.89, Q61.02, Q61.1x-Q61.8, Q26.0-Q26.39, R94.4

ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revision, Clinical Modification diagnosis codes.

Source: United States Renal Data System (USRDS). 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

Supplementary Table S3.3. ICD-9/10-CM diagnosis codes for diabetes

ICD-9-CM	250; 357.2; 362.0; 366.41
ICD-10-CM	E08.311-E08.36; E08.40; E08.42; E09.311- E09.36; E09.40; E09.42; E10.10-E13.9

ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revision, Clinical Modification diagnosis codes.

Note: We excluded ICD diagnoses related to type 1 diabetes (ICD-9-CM: 250.X1/250.X3, X=0-9; ICD-10-CM: E10) to select yearly cohorts of patients more likely to have type 2 diabetes.

Source: United States Renal Data System (USRDS). 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

Supplementary Table S3.4. ICD-9/10-CM diagnosis codes for chronic kidney disease stages

CKD stage	ICD-9-CM diagnosis codes	ICD-10-CM diagnosis codes	GFR
Stage 1	585.1	N18.1	≥ 90 ml/min/1.73 m^2
Stage 2	585.2	N18.2	60-89 ml/min/1.73 m^2
Stage 3	585.3	N18.3	30-59 ml/min/1.73 m^2
Stage 4	585.4	N18.4	15-29 ml/min/1.73 m^2
Stage 5	585.5	N18.5	<15 ml/min/1.73 m^2
Stage unknown or unspecified	016.0; 095.4; 189.0; 189.9; 223.0; 236.91; 250.4; 271.4; 283.11; 403; 404; 440.1; 442.1; 447.3; 572.4; 581-583; 585.9; 586-588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4	A18.11, A52.75, B52.0, C64.x, C68.9, D30.0x, D41.0x-D41.2x, D59.3, E08.2x, E09.2x, E10.2x, E10.65, E11.2x, E13.2x, E74.8, I12.xx, I13.0, I13.1x, I13.2, K76.7, M10.3x, M32.14, M32.15, N01.x-N08.x, N13.1, N13.1x-N13.39, N14.x,N15.0, N15.8, N15.9, N16, N18.8, N18.9, N19, N25.xx, N26.1, N26.9, O10.4xx, O12.xx, O26.83x, O90.89, Q61.02, Q61.1x-Q61.8, Q26.0-Q26.39, R94.4	

GFR, glomerular filtration rate; ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revisions, Clinical Modification diagnosis codes.

Source: United States Renal Data System (USRDS). 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

Supplementary Table S3.5. GEE model estimation for change in overall trends of glucose-lowering medication classes from 2007 to 2016 in CKD patients with type 2 diabetes

Medication Class	Parameter Estimate for Yearly Trend	95% CI		P-value
Alpha-glucosidase inhibitors	-0.01%	-0.02%	-0.01%	< 0.0001
Amylin mimetics	-0.02%	-0.03%	-0.02%	< 0.0001
Bile acid sequestrant	-0.01%	-0.01%	0.00%	0.0356
Dopamine-2 agonists	0.00%	0.00%	0.00%	0.0165
DPP-4 inhibitor	0.91%	0.88%	0.93%	< 0.0001
GLP-1 receptor agonists	0.15%	0.13%	0.16%	< 0.0001
Meglitinides	-0.08%	-0.10%	-0.07%	< 0.0001
Metformin	0.55%	0.52%	0.59%	< 0.0001
Newer insulin analogs	1.79%	1.73%	1.84%	< 0.0001
Older Insulins	-0.76%	-0.79%	-0.73%	< 0.0001
SGLT2 inhibitors	0.16%	0.15%	0.16%	< 0.0001
Sulfonylureas	-0.69%	-0.73%	-0.65%	< 0.0001
Thiazolidinediones	-1.26%	-1.28%	-1.23%	< 0.0001

CKD, chronic kidney disease; CI, confidence interval; GEE, generalized estimating equations; DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors.

Note: Parameter estimates of trends across 2007-2016 indicate the change in percent of glucose-lowering medication use per 1-year increment. We multiplied every parameter estimate and 95% confidence interval endpoint by 100, and then describe these values as percentage point differences (changes) in utilization per calendar year. For example, the model suggests an average 0.55% increase in metformin use per year. All models testing trends over time were adjusted for age, sex, race/ethnicity, CKD stage, and low-income subsidy status. Newer insulin analogs include aspart, lispro, glulisine, detemir, glargine,

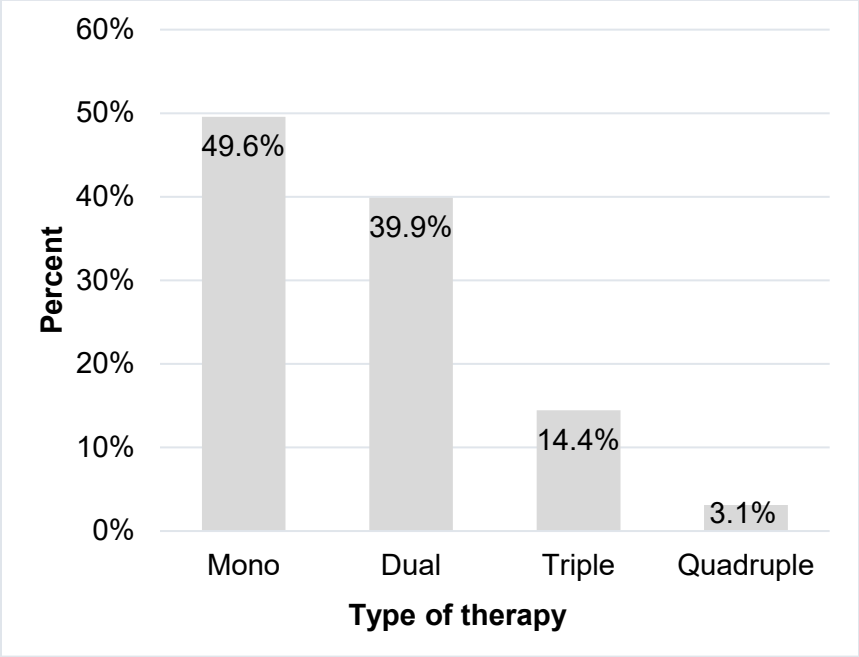
and degludec. Older insulins include human regular and neutral protamine hagedorn (NPH).

Supplementary Figure Legends

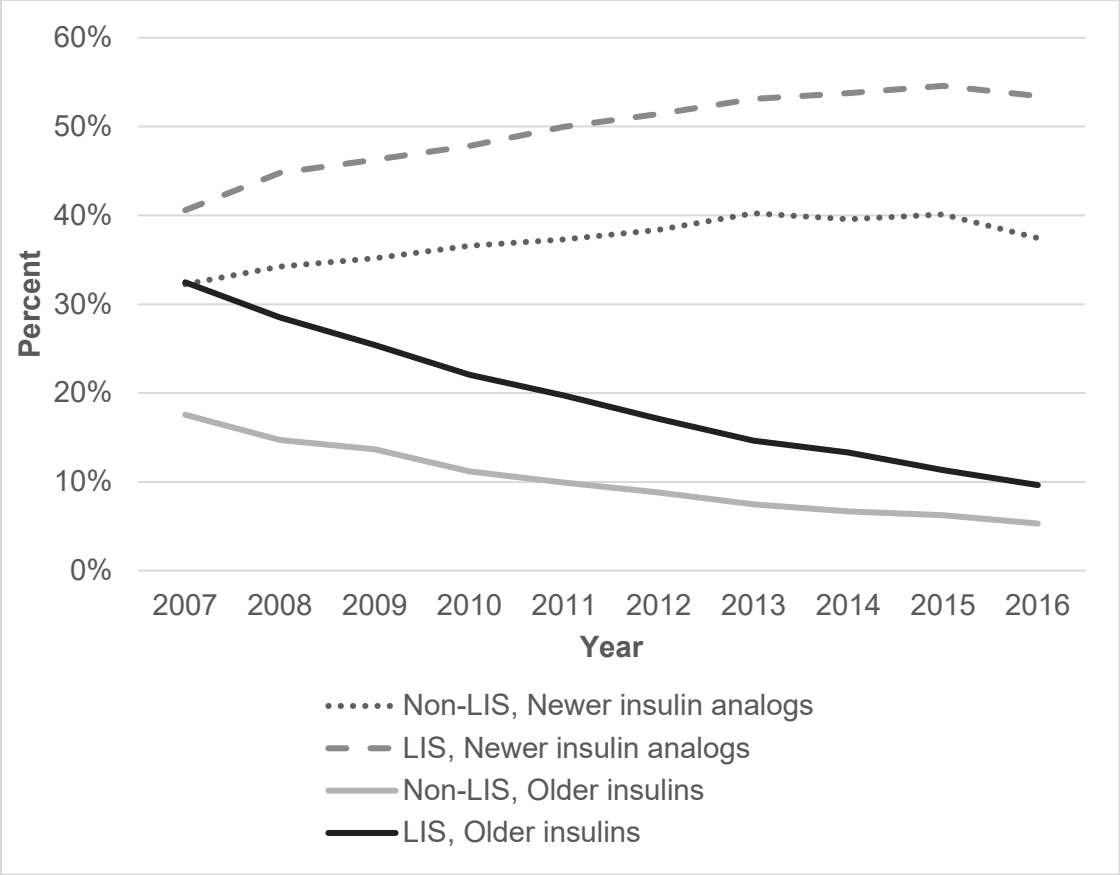
Figure S3.1. Percent using monotherapy and combination therapy among chronic kidney disease patients with type 2 diabetes using glucose-lowering medications in 2016. *Note:* All percentages do not sum up to 100%. Patients could be receiving dual, triple, or quadruple combination therapy at various periods during a year.

Figure S3.2. Trend of insulins use among chronic kidney disease patients with type 2 diabetes from 2007 to 2016, by low-income subsidy status. LIS, low-income subsidy. *Note:* Newer insulin analogs include aspart, lispro, glulisine, detemir, glargine, degludec. Older insulins include human regular and neutral protamine hagedorn (NPH).

Supplementary Figure S3.1.



Supplementary Figure S3.2.



Chapter 4

Manuscript #2: Disparities in SGLT2i or GLP-1RA Initiation among Medicare Insured Adults with CKD in the US

Disparities in SGLT2i or GLP-1RA Initiation among Medicare Insured Adults with CKD in the US

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Abstract

Background and objectives

Information regarding disparities of initiating sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with chronic kidney disease (CKD) is limited. We examined patients' sociodemographic and clinical factors associated with initiation of SGLT2i, GLP-1RA, or 2nd generation sulfonylureas in Medicare fee-for-service patient population with CKD and type 2 diabetes.

Design, setting, participants, and measurements

A retrospective cohort study using 20% random sample of Medicare fee-for-service claims was conducted. A cohort of patients with CKD and type 2 diabetes between 2013 and 2018 were created. Patients with a newly initiated prescription of SGLT2i, GLP-1RA or sulfonylurea from January 1, 2013 to December 31, 2018 were identified. Multinomial logistic regression model was used to evaluate demographic and clinical factors associated with initiation of SGLT2i, GLP-1RA, or sulfonylureas.

Results

The study cohort comprised 53,029 adults (≥18 years) with CKD and type 2 diabetes, of whom 10.0%, 17.4% and 72.6% had a first prescription for a SGLT2i, GLP-1RA, and sulfonylurea, respectively. Patients aged ≥75 years vs. 65-74 years had lower odds to start SGLT2i or GLP-1RA compared with sulfonylureas. Black patients were associated with lower odds of initiation of SGLT2i (odds ratio [OR]: 0.67, 95% confidence interval [CI]: 0.61-0.74) and GLP-1RA (OR: 0.73, 95% CI: 0.68-0.79) compared with White patients. Hispanic and Asian patients had lower odds of GLP-1RA initiation. Compared with CKD stage 3 patients, CKD stage 4-5 patients were associated with lower odds of starting

SGLT2i (OR: 0.46, 95% CI: 0.37-0.57), or GLP-1RA (OR: 0.75, 95% CI:0.67-0.85) than sulfonylureas. Patients with cardiovascular disease or hyperlipidemia had higher odds to start SGLT2i or GLP-1RA.

Conclusions

The results of this study identified disparities in use of SGLT2i and GLP-1RA in CKD patients. Black and older patients were significantly less likely to be initiated on SGLT2i or GLP-1RA than sulfonylureas.

Introduction

An estimated 15% of US adults (≥18 years) (37 million people) have chronic kidney disease (CKD). [1] Diabetes is the leading cause of CKD.[2] Large clinical trials have shown benefits of newer glucose-lowering medications on cardiovascular and kidney outcomes in CKD patients with type 2 diabetes.[3–12] Sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) are recommended in CKD patients with type 2 diabetes by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) clinical guideline.[13,14]

Although evidence of cardiovascular and kidney benefits from clinical trials evaluating SGLT2i and GLP-1RA is overwhelming, prescription of these newer glucose-lowering medications is low. A recent retrospective study with Medicare claims data showed that SGLT2i and GLP-1RA were only used in 3.3% and 6.1% of patients with CKD and type 2 diabetes, respectively, in 2016.[15] Another retrospective analysis using 2015-2019 data from the Optum Clinformatics Data Mart also suggested that prescription of SGLT2i was low in commercially insured patients with type 2 diabetes and showed racial/ethnic, gender, and socioeconomic disparities in receipt of SGLT2i therapy, but CKD status was not evaluated.[16]

While benefits of SGLT2i and GLP-1RA among patients with type 2 diabetes and CKD have been demonstrated, there is no evidence showing cardiovascular and kidney benefits of older glucose-lowering medications like sulfonylureas in this population, but they are widely used[15]. The second-generation agents (glyburide, glipizide, glimepiride) have become popular, due to lower risk of hypoglycemia.

Our study aimed to examine whether patients with CKD and type 2 diabetes were more likely to start SGLT2i and GLP-1RA, compared with sulfonylureas in a more recent Medicare fee-for-service population. We also examined patients' sociodemographic and clinical factors associated with initiation of SGLT2i, GLP-1RA, or sulfonylureas (2nd generation).

Materials and Methods

Data source

We used data from a 20% random sample of Medicare fee-for-service claims. To conduct this study, claims data files included patient demographic characteristics, health insurance enrollment, institutional (inpatient, outpatient, home health, skilled nursing facility), physician visits, and Part D characteristics files (including prescription events) from January 1, 2012 to December 31, 2018.

Study design and cohort selection

We conducted a retrospective cohort study design in CKD patients with type 2 diabetes. We identified patients with CKD and type 2 diabetes from 2013 to 2018, and used International Classification of Disease, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) diagnosis codes provided by the United States Renal Data System (USRDS).[17] We excluded diagnoses related to type 1 diabetes (ICD-9-CM: 250.X1/250.X3, X=0-9; ICD-10-CM: E10) to select patients more likely to have type 2

diabetes. Patients were considered as having type 2 diabetes if they had ≥ 1 diagnosis code from inpatient services, home health, or skilled nursing facilities, or ≥ 2 diagnosis codes from physician claims or outpatient services on different dates within 365 days. The same method was used to identify CKD patients. This method has been shown to increase sensitivity and specificity compared with using only one claim.[18] The first claim date was chosen for confirmed diagnosis.

To establish CKD and type 2 diabetes diagnoses, the index date was defined by choosing the claims date for the later of the two diagnoses. For example, if the diabetes date was June 15, 2013, and the CKD date was July 12, 2014, then the diagnosis index date was July 12, 2014. Patients < 18 years old at the diagnosis index date were excluded. Next, we identified patients who filled a first prescription of SGLT2i, GLP-1RA or sulfonylurea from January 1, 2013 to December 31, 2018. The first prescription date of SGLT2i, GLP-1RA or sulfonylureas after the CKD and diabetes diagnosis index date was the prescription index date. We then created three mutually exclusive new user groups: SGLT2i, GLP-1RA and sulfonylureas. For each treatment group, we excluded patients who had a prescription for any of the drugs of interest (SGLT2i, GLP-1RA or sulfonylureas) in the 12-month period before the prescription index fill date. We then applied the following inclusion criteria: continuous enrollment in Medicare Part A, Part B and Part D in one year before or on the prescription index date.

Study outcome

The outcome of the study was initiation of glucose-lowering medications prescriptions (**Supplementary Table S4.1**).

Study covariates

To define the study covariates, we used a 1-year baseline period before the prescription index date. The covariates included age, gender, race/ethnicity, region (Northeast, Midwest, South, and West), income level, health insurance status, baseline glucose-lowering medications prescriptions, CKD stage status, and comorbid conditions. Zip code level household median income from the US Census Bureau (a community-level characteristic) was used to approximate personal income level. Low-income subsidy (LIS) status was included as a proxy measure of personal lower income status. The Medicare Part D program offers LIS benefits to enrollees with limited assets and income. Comorbid conditions were based on Elixhauser measures [19], and confirmed if at least one inpatient or two physician/outpatient services claims on different days were identified during the baseline period. A comorbid condition index score was calculated based on van Walraven's method.[20] Because laboratory-based information was not available in our data files, kidney function was defined by CKD stage-specific ICD-9/10-CM diagnosis codes (**Supplementary Table S4.2**) from outpatient or physician visit claims in the baseline period. The last claim code for the CKD stage (1 to 5) in the baseline period was selected.

Statistical analysis

We described baseline characteristics across individuals who initiated SGLT2i, GLP-1RA or sulfonylureas (count and percentage for categorical variables and mean for continuous variables). We used multinomial logistic regression models to evaluate factors associated with initiation of SGLT2i and GLP-1RA compared with sulfonylureas. Estimated adjusted odds ratios are reported with 95% confidence intervals. All statistical

testing was 2-tailed, with p-values < .05 designated as statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

This study was approved by the Hennepin Healthcare Human Subjects Research Committee. A waiver of consent was issued due to data anonymity and large secondary data study.

Results

After applying study inclusion and exclusion criteria, the study cohort comprised 53,029 adults (≥18 years) with CKD and type 2 diabetes, of whom 10.0% (n=5,277) had a prescription for a SGLT2i, 17.4% (n=9,252) with a GLP-1RA, and 72.6% (n=38,500) with a sulfonylurea. A CONSORT diagram for patient selection is provided in **Figure 4.1**. The overall mean age (SD) was 71.4 (±10.9) years; SGLT2i and GLP-1RA users were younger than sulfonylureas users. Baseline insulin use was 47.5%, 69.7% and 21.0% of patients among users of SGLT2i, GLP-1RA, and sulfonylureas, respectively. Baseline characteristics of each treatment group are summarized in **Table 4.1**.

Demographic differences in initiating SGLT2i and GLP-1RA versus sulfonylureas

After adjusting demographic and clinical factors (**Table 4.2**), patients aged ≥75 years vs. 65-74 years had lower odds to start SGLT2i or GLP-1RA compared with sulfonylureas. Females had higher odds to initiate GLP-1RA (odds ratio [OR]: 1.2, 95% confidence interval [CI]: 1.13-1.26) than males, but lower odds to initiate SGLT2i (OR: 0.88, 95% CI: 0.83-0.94). Black race was associated with lower odds of initiation of SGLT2i (OR: 0.67, 95% CI: 0.61-0.74) or GLP-1RA (OR: 0.73, 95% CI: 0.68-0.79)

compared with White race. Hispanic and Asian patients had lower odds of initiation of GLP-1RA. Higher median household zip-code income greater than or equal to $100,000 was associated with higher odds of initiation of GLP-1RA vs. $60,000 to $99,999 (OR: 1.21, 95% CI: 1.10-1.35). LIS status was not associated with initiation of either SGLT-2i or GLP-1RA. Compared with patients living in the Midwest region, people living in the Northeast, South, or West had higher odds to start SGLT2i. There was no significant difference between regions in initiation of GLP-1RA.

Clinical difference in initiating SGLT2i and GLP-1RA versus sulfonylureas

Patients with baseline insulin use had higher odds to initiate SGLT2i (OR: 3.78; 95% CI: 3.54- 4.04) or GLP-1RA (OR: 8.58; 95% CI: 8.11-9.07) compared to sulfonylureas. Baseline metformin use was associated with higher odds of initiating SGLT2i (OR: 1.15, 95% CI: 1.07-1.23), but lower odds of initiating GLP-1RA (OR: 0.85, 95% CI: 0.80- 0.90).

We also examined the odds of starting SGLT2i or GLP-1RA based on clinical characteristics. Compared with CKD stage 3 patients, CKD stage 4-5 patients had lower odds of starting SGLT2i (OR: 0.46, 95% CI: 0.37-0.57), or GLP-1RA (OR: 0.75, 95% CI:0.67-0.85) than sulfonylureas, but CKD stage 1-2 patients were associated with higher odds of starting SGLT2i (OR: 1.80, 95% CI: 1.62-2.01). Patients with a history of cardiovascular disease or hyperlipidemia had higher odds to start SGLT2i or GLP-1RA. For the Elixhauser comorbidity score, a higher value was associated with a lower odds of starting SGLT2i (OR: 0.96, $p < 0.0001$) or GLP-1RA (OR: 0.96, $p < 0.0001$).

Subgroup analysis among patients with LIS

Results were similar in the subgroup analysis among patients with LIS (**Supplementary Table S4.3**). Patients aged ≥75 years, Black race, CKD stage 4-5, and a higher Elixhauser comorbidity score were associated with lower odds of initiation of SGLT2i or GLP-1RA.

Discussion

Our study is the first study in adult patients with CKD and type 2 diabetes using Medicare claims to compare initiation of SGLT2i and GLP-1RA with sulfonylureas across race, age, gender and socioeconomic factors. Black race was associated with a significantly lower rate of SGLT2i and GLP-1RA use, while Hispanic ethnicity and Asian race were associated with a significantly lower rate of GLP-1RA use compared to Whites. Also, there was significant differences in age, gender, socioeconomic, and clinical status of patients initiating SGLT2i and GLP-1RA compared with sulfonylureas.

We observed racial/ethnic differences in initiation of SGLT2i and GLP-1RA, with Blacks significantly less likely to start SGLT2i or GLP-1RA compared to Whites even after adjustment for community socioeconomic status and clinical factors. Hispanic and Asian ethnicity/race was also associated with lower odds of initiation of GLP-1RA. However, Asian race was associated with higher odds of initiation of SGLT2i. The subgroup analysis among patients with LIS also demonstrated similar race/ethnicity disparity in initiating SGLT2i and GLP-1RA compared with sulfonylureas; Blacks were significantly less likely to initiate newer agents. A recent published study examined racial differences in glycemic control among older adults (≥65 years) living with type 2

diabetes using National Health and Nutrition Examination Survey (NHANES) 2003–2014 data.[21] Researchers reported that non-Hispanic Blacks and Mexican Americans had increasing trends in mean hemoglobin A1c (HbA1c) over time, whereas non-Hispanic Whites showed decreasing HbA1c over time. Poor glycemic control in non-Hispanic Blacks and Mexican Americans over time may reflect lower use of newer glucose-lowering medications among these populations. The DAPA-CKD trial was specially designed to focus on patients with CKD, and enrolled 4,304 patients with an estimated glomerular filtration rate (eGFR) 25–75 ml/min per 1.73 m^2 and a urinary albumin-to-creatinine ratio ACR ≥ 200 mg/g (20 mg/mmol).[6] Dapagliflozin was shown to significantly reduce the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from kidney or cardiovascular causes. The benefit of dapagliflozin on the primary outcome was also shown in the Black subgroup (hazard ratio, 0.33; 95% CI: 0.13-0.81).

In addition to racial differences in use of SGLT2i or GLP-1RA, we discovered differences in use based on gender, socioeconomic status and region. Interestingly, female patients were less likely to start SGLT2i, but more likely to start GLP-1RA compared with male patients. These findings were consistent with another published study in the non-CKD population.[22] Those with a median household income of greater than or equal to $100,000 were more likely receive GLP-1RA than those with a median income ranging from $60,000 to $99,999. We didn't observe a significant difference in starting SGLT2i or GLP-1RA based on LIS status. Canagliflozin is one of 200 drugs with the highest utilization by dual eligible patients having both Medicare and Medicaid benefits.[23] They are a particularly vulnerable population-86% have annual incomes below

150 percent of the Federal poverty level. However, canagliflozin was included on <75% of Part D plan formularies in 2019 and 2020.[23,24] Low rate of formulary inclusion may limit patient access to certain glucose-lowering medications.

Two recent studies analyzed use of SGLT2i based on sociodemographic and clinical factors. Both of the studies focused on commercially insured and Medicare Advantage non-CKD patients. Eberly et al. compared adult patients with type 2 diabetes who received and did not receive SGLT2i treatment using the Optum Clinformatics Data Mart from October 1, 2015, to June 30, 2019.[16] Black race, Asian race, and female gender were associated with lower rates of adoption of SGLT2i, whereas higher median household income (≥$100,000, and $50,000-$99, 999 vs <$50, 000) was associated with a higher rate of adoption of SGLT2i. A greater number of Elixhauser comorbidities was associated with a lower rate of SGLT2i use. The study focused on adoption of SGLT2i and did not study GLP-1RA use in adult patients with type 2 diabetes with a younger median age than our study. Investigators evaluated comorbidities from the earliest date of available data to the date of cohort entry. Some patients may have had a relatively short baseline evaluation period, which could induce bias in terms of number or type of comorbid conditions. Using a similar cohort design and same dataset, McCoy et al. examined adult patients (≥18 years) with type 1 or 2 diabetes for use of SGLT2i treatment between 2013 and 2016.[25] They also showed that SGLT2i users were younger, and SGLT2i were prescribed less frequently to women versus men, and Black versus White patients. Compared with patients living in the Midwest, patients living in all other U.S. regions were more likely to start a SGLT2i, with the highest probability among

patients living in the South. Both the studies showed that visit to an endocrinologist was strongly associated with SGLT2i initiation.

Five large randomized clinical trials (EMPAREG, CANVAS, DECLARE, CREDENCE, and DAPA-CKD) demonstrated cardiovascular benefits, and kidney protective benefits of SGLT2i.[3–6,9,10,26] The CREDENCE and DAPA-CKD trials specifically enrolled a large population with type 2 diabetes and CKD with high albuminuria levels and focused on kidney-related outcomes, but their results were released in 2019 and 2020, and would not have been expected to impact our study findings. The clinical trials that may have impacted our results were the CANVAS (canagliflozin, published 2017), EMPAREG (empagliflozin, 2015), SUSTAIN-6 (semaglutide, 2016) and LEADER (liraglutide, 2016), all of which demonstrated significant cardiovascular and kidney benefits of SGLT-2i and GLP-1RA.[3,9–12] Although enrolled participants in these four clinical trials were type 2 diabetes patients, they all included some patients with eGFR below 60, and their primary outcome was MACE (i.e., a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. We observed that CKD patients with cardiovascular disease had significantly higher initiation of SGLT2i or GLP-1RA than sulfonylureas.

Consistent with other studies, we noted that older patients were significantly less likely to start SGLT2i or GLP-1RA than sulfonylureas compared to younger patients. Older patients may be more likely to have multiple comorbidities, polypharmacy and financial barriers for new expensive medications which may lead inertia in initiating novel medications. Nevertheless, significant benefits of SGLT2i were shown among the

subgroup patients (≥65 years) in the study of EMPAREG, CANVAS, DECLARE, and DAPA-CKD.[4–6,9,10,26]

Our study has several strengths. We provide a comparison between initiations of novel, tradename glucose-lowering medications vs. generic sulfonylureas in adults with CKD and type 2 diabetes enrolled in Medicare Part D coverage. Sulfonylureas are commonly used glucose-lowering agents and generically available, but do not have demonstrated cardiovascular or kidney benefits in CKD patients. Also, we used a new user design, which reduces the risk of selection bias that can occur when patients have been exposed to a drug class in the past. The Medicare claims database is large enough to create a population for more than 53,000 patients meeting study criteria. It provides comprehensive information on patient demographics, inpatient and outpatient diagnoses and procedures, and prescriptions. We used actual medication claims dispensing records rather than other data sources that might measure only prescribing patterns.

Our analysis also has limitations. Clinical characteristics were measured based on administrative claims. In our study, CKD stage and evidence of patients with CKD and type 2 diabetes, were identified with diagnosis codes, and could not be verified through medical record review or laboratory values. We used ≥1 inpatient claim or ≥ 2 physician/outpatient claims to increase sensitivity and specificity.[18] Our analysis cohort consisted of CKD patients enrolled in Medicare Part D coverage, so utilization patterns may differ for patients enrolled in non-Part D prescription plans or Medicare Advantage plans or other types of health insurance. The Medicare data set does not include patients aged younger than 65 years, except for people with disabilities. Finally, zip code level household median income was used to approximate personal income level.

Conclusions

The results of this study identified disparities in use of SGLT2i and GLP-1RA among Medicare insured adults diagnosed with type 2 diabetes and CKD. These new medications have been demonstrated to improve kidney and cardiovascular outcomes across race groups and in older patients with diabetes, CKD and heart failure. Black patients and older patients were significantly less likely to be initiated on SGLT2i or GLP-1RA than sulfonylureas. Hispanic and Asian patients were also associated with lower odds of initiation of GLP-1RA. This represents a health disparity issue that needs to be addressed to slow kidney disease progression in populations that are at higher risk of progressing to end stage kidney disease. These findings should be also be a call for public education and political action by kidney disease patient advocacy organizations such as the National Kidney Foundation and American Association of Kidney Patients to eliminate health disparities in the prescription and to promote use of these newer diabetes agents which have been shown to slow the rate of CKD progression.

Article Information Section

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Table 4.1. Baseline characteristics of CKD patients aged ≥ 18 years with type 2 diabetes, Medicare 20% CKD claims, 2012-218

Baseline characteristics	Overall cohort	SGLT2i	GLP-1RA	Sulfonylurea
Total (n)	53029	5277	9252	38500
Age				
mean (std), year	71.4 (10.9)	68.8 (10.6)	66.8 (10.6)	72.9 (10.6)
median (IQR),year	72.0 (66.0, 78.0)	70.0 (65.0, 75.0)	68.0 (61.0, 73.0)	73.0 (67.0, 80.0)
Age category, years				
18-64 y	10262 (19.4%)	1284 (24.3%)	2903 (31.4%)	6075 (15.8%)
65-74 y	22090 (41.7%)	2531 (48.0%)	4387 (47.4%)	15172 (39.4%)
75-84 y	15137 (28.5%)	1201 (22.8%)	1703 (18.4%)	12233 (31.8%)
>= 85 y	5540 (10.4%)	261 (4.9%)	259 (2.8%)	5020 (13.0%)
Sex				
Male	25951 (48.9%)	2779 (52.7%)	4156 (44.9%)	19016 (49.4%)
Female	27078 (51.1%)	2498 (47.3%)	5096 (55.1%)	19484 (50.6%)
Race/Ethnicity				
White	40368 (76.1%)	4034 (76.4%)	6999 (75.6%)	29335 (76.2%)
Black	7491 (14.1%)	580 (11.0%)	1364 (14.7%)	5547 (14.4%)
Asian	1489 (2.8%)	208 (3.9%)	191 (2.1%)	1090 (2.8%)
Hispanic	1815 (3.4%)	226 (4.3%)	350 (3.8%)	1239 (3.2%)
Other/unknown	1866 (3.5%)	229 (4.3%)	348 (3.8%)	1289 (3.3%)
Region				
Midwest	12043 (22.7%)	993 (18.8%)	2079 (22.5%)	8971 (23.3%)
Northeast	9306 (17.5%)	930 (17.6%)	1647 (17.8%)	6729 (17.5%)
South	22548 (42.5%)	2243 (42.5%)	3941 (42.6%)	16364 (42.5%)
West	9031 (17.0%)	1107 (21.0%)	1580 (17.1%)	6344 (16.5%)
Other/unknown	101 (0.2%)	*	*	92 (0.2%)
Low income subsidy (LIS) status				
Non-LIS	30075 (56.7%)	2821 (53.5%)	4477 (48.4%)	22777 (59.2%)
LIS	22954 (43.3%)	2456 (46.5%)	4775 (51.6%)	15723 (40.8%)

Zip code level Household median income				
<=$34,999	3644 (6.9%)	357 (6.8%)	643 (6.9%)	2644 (6.9%)
$35,000-59,999	25870 (48.8%)	2519 (47.7%)	4579 (49.5%)	18772 (48.8%)
$60,000-99,999	18008 (34.0%)	1856 (35.2%)	3050 (33.0%)	13102 (34.0%)
>=$100,000	4293 (8.1%)	435 (8.2%)	765 (8.3%)	3093 (8.0%)
Missing	1214 (2.3%)	110 (2.1%)	215 (2.3%)	889 (2.3%)
CKD stage				
1/2	4923 (9.3%)	640 (12.1%)	922 (10.0%)	3361 (8.7%)
3	18320 (34.5%)	1323 (25.1%)	3319 (35.9%)	13678 (35.5%)
4/5	3720 (7.0%)	98 (1.9%)	632 (6.8%)	2990 (7.8%)
Unk/Unspc	26066 (49.2%)	3216 (60.9%)	4379 (47.3%)	18471 (48.0%)
ESKD	1465 (2.8%)	14 (0.3%)	300 (3.2%)	1151 (3.0%)
Metformin	30674 (57.8%)	3529 (66.9%)	4941 (53.4%)	22204 (57.7%)
Meglitinides	1096 (2.1%)	159 (3.0%)	252 (2.7%)	685 (1.8%)
Thiazolidinediones	2948 (5.6%)	491 (9.3%)	587 (6.3%)	1870 (4.9%)
Alpha-glucosidase inhibitors	220 (0.4%)	26 (0.5%)	56 (0.6%)	138 (0.4%)
Bile acid sequestrants	412 (0.8%)	69 (1.3%)	102 (1.1%)	241 (0.6%)
Dopamine-2 agonists	31 (0.1%)	*	*	22 (0.1%)
DPP-4i	11607 (21.9%)	1827 (34.6%)	2279 (24.6%)	7501 (19.5%)
Amylin mimetics	43 (0.1%)	*	29 (0.3%)	*
Insulins	17059 (32.2%)	2504 (47.5%)	6451 (69.7%)	8104 (21.0%)
Cardiovascular disease	35213 (66.4%)	3261 (61.8%)	6006 (64.9%)	25946 (67.4%)
Hypertension	49392 (93.1%)	4896 (92.8%)	8708 (94.1%)	35788 (93.0%)
Hyperlipidemia	42224 (79.6%)	4434 (84.0%)	7658 (82.8%)	30132 (78.3%)
Hypoglycemia events	3738 (7.0%)	369 (7.0%)	925 (10.0%)	2444 (6.3%)
Number of ELIXHAUSER comorbidity conditions				
mean (std)	6.6 (3.3)	6.0 (3.0)	6.7 (3.1)	6.7 (3.4)
median (IQR)	6.0 (4.0, 9.0)	5.0 (4.0, 8.0)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)
ELIXHAUSER Comorbidity Index Score				
mean (std)	10.2 (10.0)	7.3 (8.8)	8.2 (9.1)	11.1 (10.2)

median (IQR)	8.0 (3.0, 16.0)	5.0 (0.0, 12.0)	6.0 (1.0, 14.0)	9.0 (4.0, 17.0)

CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; IQR, interquartile range; SGLT2i, sodium-glucose cotransporter 2 inhibitors; std, standard deviation; Unk/unspc, CKD stage unknown or unspecified.

Note: * refers to counts of 10 or fewer patients.

Table 4.2. Factors associated with initiating SGLT2i, or GLP-1RA compared with sulfonylureas, multinomial logistic regression analysis

	SGLT2i vs. Sulfonylureas				GLP-1RA vs. Sulfonylureas			
Characteristics	Adjusted odd ratios	95% CI		p-values	Adjusted odd ratios	95% CI		p-values
Age category, years								
18-64 y	1.31	1.20	1.43	<.0001	1.55	1.44	1.67	<.0001
65-74 y	1.00				1.00			
75-84 y	0.63	0.59	0.68	<.0001	0.53	0.49	0.56	<.0001
>= 85 y	0.39	0.34	0.45	<.0001	0.21	0.18	0.24	<.0001
Sex								
Male					1.00			
Female	0.88	0.83	0.94	<.0001	1.20	1.13	1.26	<.0001
Race/Ethnicity								
White	1.00				1.00			
Black	0.67	0.61	0.74	<.0001	0.73	0.68	0.79	<.0001
Asian	1.23	1.04	1.46	0.0181	0.74	0.62	0.88	0.0008
Hispanic	0.98	0.84	1.16	0.844	0.81	0.70	0.93	0.0039
Other/unknown	1.03	0.88	1.20	0.7021	0.94	0.82	1.08	0.3592
Region								
Midwest	1.00				1.00			
Northeast	1.18	1.07	1.31	0.0012	1.09	1.00	1.18	0.0497
South	1.22	1.12	1.32	<.0001	1.03	0.96	1.10	0.3846
West	1.46	1.32	1.61	<.0001	1.08	0.99	1.18	0.0737
Other/unknown	0.32	0.11	0.92	0.0346	0.18	0.07	0.48	0.0005
Low income subsidy (LIS)	1.01	0.94	1.09	0.7775	0.98	0.92	1.05	0.5855
Zip code level Household median income								
<=$34,999	0.95	0.84	1.09	0.4939	0.87	0.78	0.98	0.0175
$35,000-59,999	0.94	0.88	1.01	0.0739	0.94	0.88	1.00	0.0401
$60,000-99,999	1.00				1.00			

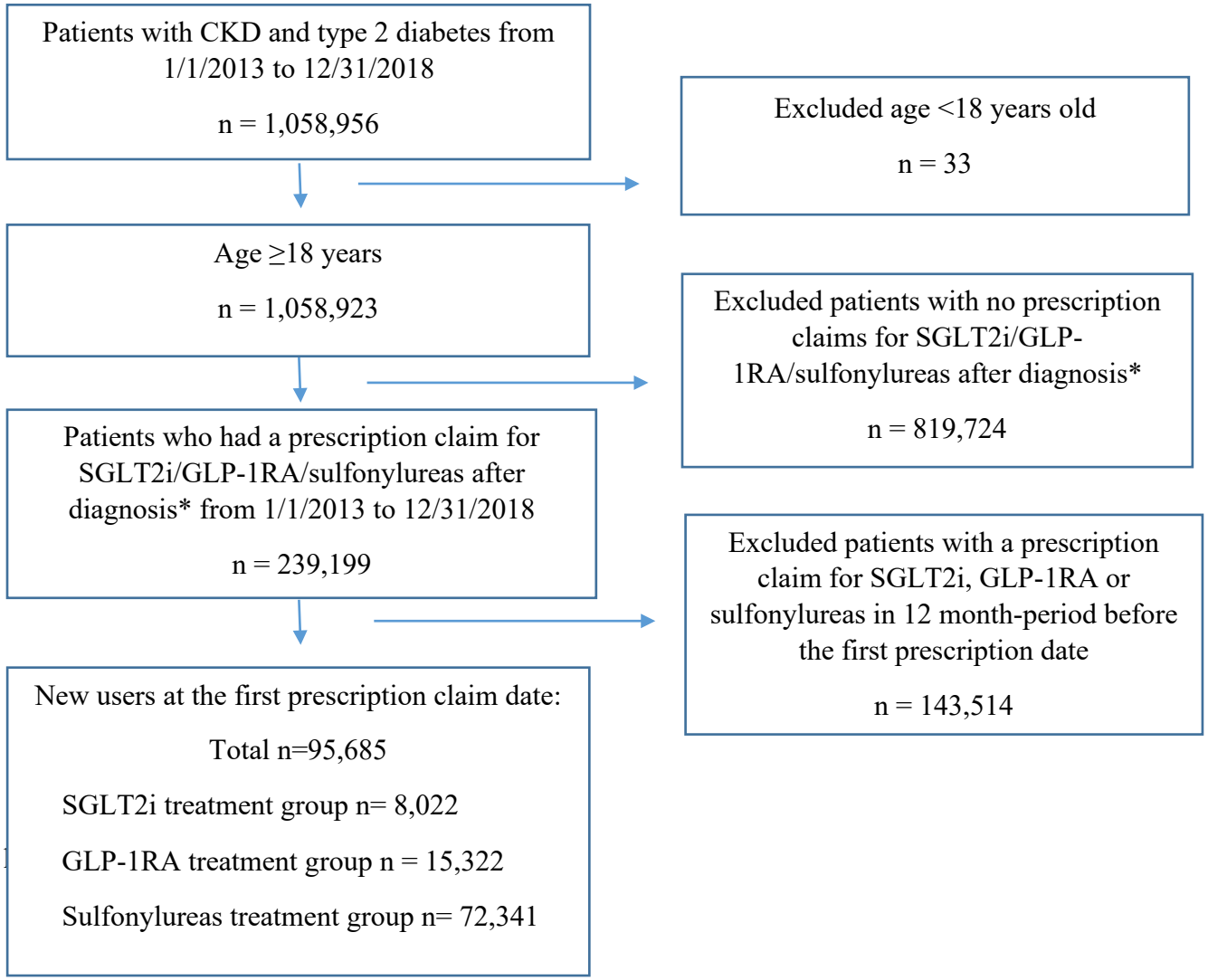
>=$100,000	0.97	0.86	1.10	0.6498	1.21	1.10	1.35	0.0002
Missing	0.78	0.63	0.97	0.0283	0.89	0.75	1.07	0.2196
CKD stage								
1/2	1.80	1.62	2.01	<.0001	1.08	0.99	1.19	0.0938
3	1.00				1.00			
4/5	0.46	0.37	0.57	<.0001	0.75	0.67	0.85	<.0001
Unk/Unspc	1.61	1.50	1.73	<.0001	0.87	0.82	0.93	<.0001
ESKD	0.15	0.09	0.26	<.0001	0.74	0.63	0.89	0.0008
Metformin use	1.15	1.07	1.23	<.0001	0.85	0.80	0.90	<.0001
Meglitinides use	1.62	1.34	1.96	<.0001	1.76	1.48	2.09	<.0001
Thiazolidinediones use	1.85	1.65	2.07	<.0001	1.47	1.32	1.64	<.0001
Alpha-glucosidase inhibitors use	0.94	0.61	1.47	0.7994	1.22	0.85	1.74	0.2908
Bile acid sequestrants use	2.11	1.58	2.82	<.0001	1.96	1.50	2.56	<.0001
DPP-4i use	2.15	2.01	2.30	<.0001	1.47	1.38	1.57	<.0001
Insulin use	3.78	3.54	4.04	<.0001	8.58	8.11	9.07	<.0001
Cardiovascular disease	1.08	1.00	1.16	0.0407	1.13	1.06	1.20	0.0002
Hypertension	1.11	0.98	1.25	0.1104	1.16	1.03	1.29	0.0112
Hyperlipidemia	1.39	1.28	1.51	<.0001	1.22	1.14	1.31	<.0001
Hypoglycemia events	1.00	0.88	1.13	0.9668	1.05	0.96	1.15	0.3212
ELIXHAUSER Comorbidity Index Score	0.96	0.96	0.97	<.0001	0.96	0.96	0.97	<.0001
Year of prescription	1.34	1.31	1.37	<.0001	1.40	1.38	1.43	<.0001

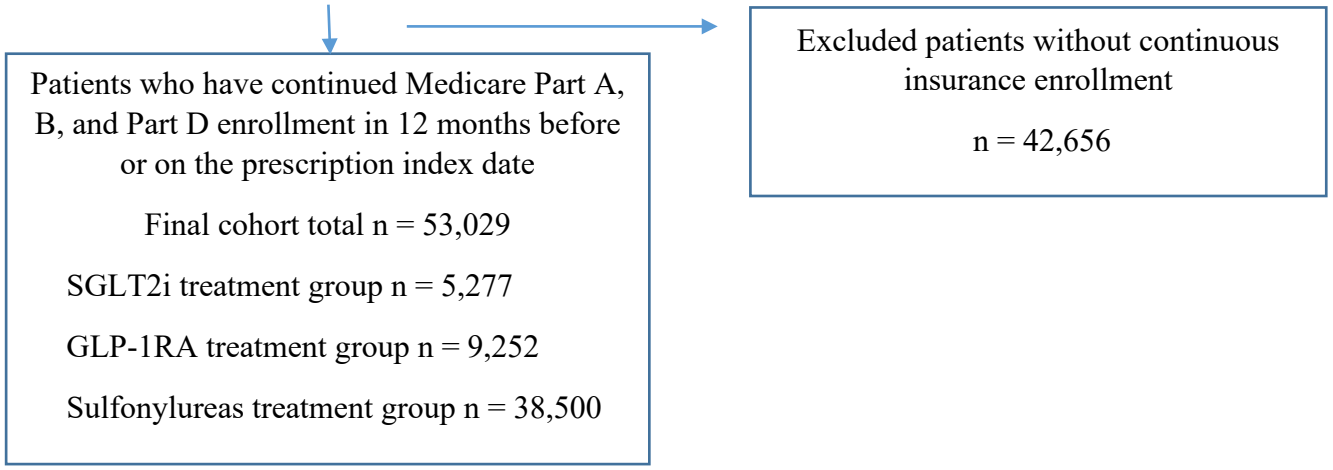
CKD, chronic kidney disease; CI, confidence interval; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; Unk/unspc, CKD stage unknown or unspecified.

Figure Legends

Figure 4.1. CONSORT diagram for patient selection. CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors. *Note:* *Diagnosis is defined as patients with CKD and type 2 diabetes.

Figure 4.1.


Patients with CKD and type 2 diabetes from 1/1/2013 to 12/31/2018
n = 1,058,956
Excluded age <18 years old
n = 33
Age ≥18 years
n = 1,058,923
Excluded patients with no prescription claims for SGLT2i/GLP-1RA/sulfonylureas after diagnosis*
n = 819,724
Patients who had a prescription claim for SGLT2i/GLP-1RA/sulfonylureas after diagnosis* from 1/1/2013 to 12/31/2018
n = 239,199
Excluded patients with a prescription claim for SGLT2i, GLP-1RA or sulfonylureas in 12 month-period before the first prescription date
n = 143,514
New users at the first prescription claim date:
Total n=95,685
SGLT2i treatment group n= 8,022
GLP-1RA treatment group n = 15,322
Sulfonylureas treatment group n= 72,341


Patients who have continued Medicare Part A, B, and Part D enrollment in 12 months before or on the prescription index date
Final cohort total n = 53,029
SGLT2i treatment group n = 5,277
GLP-1RA treatment group n = 9,252
Sulfonylureas treatment group n = 38,500
Excluded patients without continuous insurance enrollment
n = 42,656

Supplementary Material

Table S4.1. Description of investigated glucose-lowering medications prescriptions in the study

Table S4.2. Chronic kidney disease stage-specific ICD-9/10-CM diagnosis codes

Table S4.3. Factors associated with initiating SGLT2i, or GLP-1RA compared with Sulfonylurea among CKD and type 2 diabetes patients with low income subsidy, multinomial logistic regression analysis

Supplementary Table S4.1. Description of investigated glucose-lowering medications prescriptions in the study

Class	Medication	FDA approval date
Sulfonylureas (2nd generation)	glipizide	2002
	glyburide	2002
	glimepiride	1999
SGLT2i	canagliflozin	2013
	dapagliflozin	2014
	empagliflozin	2014
	ertugliflozin	2017
GLP-1RA	albiglutide	2014
	dulaglutide	2014
	exenatide	2005
	exenatide extended-release	2012
	liraglutide	2010
	lixisenatide	2016
	semaglutide	2017

FDA, the Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Supplementary Table S4.2. Chronic kidney disease stage-specific ICD-9/10-CM diagnosis codes

CKD stage	ICD-9-CM diagnosis codes	ICD-10-CM diagnosis codes	GFR
Stage 1	585.1	N18.1	≥90 ml/min/1.73 m^2
Stage 2	585.2	N18.2	60-89 ml/min/1.73 m^2
Stage 3	585.3	N18.3	30-59 ml/min/1.73 m^2
Stage 4	585.4	N18.4	15-29 ml/min/1.73 m^2
Stage 5	585.5 or 585.6	N18.5 or N18.6	<15 ml/min/1.73 m^2

CKD, chronic kidney disease; GFR, glomerular filtration rate; ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revisions, Clinical Modification diagnosis codes.

Source: United States Renal Data System (USRDS). 2020 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

Supplementary Table S4.3. Factors associated with initiating SGLT2i, or GLP-1RA compared with sulfonylureas among CKD and type 2 diabetes patients with low income subsidy (N=22,954), multinomial logistic regression analysis

	SGLT2i vs. Sulfonylureas				GLP-1RA vs. Sulfonylureas			
Characteristics	Adjusted odd ratios	95% CI		p-values	Adjusted odd ratios	95% CI		p-values
Age category, years								
18-64 y	1.50	1.35	1.67	<.0001	1.78	1.63	1.95	<.0001
65-74 y	1.00				1.00			
75-84 y	0.70	0.61	0.79	<.0001	0.59	0.52	0.66	<.0001
>= 85 y	0.46	0.37	0.57	<.0001	0.26	0.21	0.33	<.0001
Sex								
Male	1.00				1.00			
Female	1.04	0.95	1.14	0.4212	1.32	1.22	1.43	<.0001
Race/Ethnicity								
White	1.00				1.00			
Black	0.60	0.52	0.68	<.0001	0.71	0.65	0.78	<.0001
Asian	1.24	1.02	1.52	0.0324	0.86	0.70	1.05	0.1423
Hispanic	1.00	0.84	1.19	0.9783	0.86	0.74	1.00	0.0522
Other/unknown	0.88	0.71	1.11	0.2850	0.81	0.66	0.99	0.0359
Region								
Midwest	1.00				1.00			
Northeast	1.07	0.92	1.25	0.4024	0.95	0.84	1.07	0.3812
South	1.06	0.93	1.21	0.3697	0.82	0.75	0.91	0.0001
West	1.26	1.09	1.47	0.0023	0.81	0.71	0.92	0.0008
Other/unknown	0.67	0.13	3.45	0.6313	0.15	0.02	1.25	0.0791
CKD stage								
1/2	1.89	1.60	2.22	<.0001	1.13	0.98	1.29	0.0978
3	1.00				1.00			

4/5	0.42	0.31	0.58	<.0001	0.78	0.66	0.93	0.0041
Unk/Unspc	1.56	1.40	1.75	<.0001	0.85	0.78	0.93	0.0004
ESKD	0.18	0.09	0.33	<.0001	0.76	0.61	0.94	0.0099
Metformin use	1.06	0.97	1.17	0.2136	0.82	0.76	0.89	<.0001
Meglitinides use	1.53	1.13	2.07	0.0058	1.76	1.34	2.31	<.0001
Thiazolidinediones use	1.67	1.40	1.99	<.0001	1.25	1.06	1.48	0.0096
Alpha-glucosidase inhibitors use	0.71	0.38	1.33	0.2838	1.19	0.75	1.89	0.4643
Bile acid sequestrants use	2.44	1.58	3.78	<.0001	2.10	1.40	3.16	0.0003
DPP-4i use	2.53	2.29	2.79	<.0001	1.60	1.47	1.76	<.0001
Insulins use	3.69	3.36	4.06	<.0001	8.82	8.11	9.59	<.0001
Cardiovascular disease	1.06	0.95	1.18	0.3093	1.11	1.01	1.22	0.028
Hypertension	1.19	0.99	1.43	0.0712	1.25	1.06	1.48	0.008
Hyperlipidemia	1.29	1.15	1.45	<.0001	1.20	1.09	1.32	0.0003
Hypoglycemia events	0.99	0.84	1.17	0.9420	1.00	0.89	1.13	0.9719
ELIXHAUSER Comorbidity Index Score	0.96	0.96	0.97	<.0001	0.97	0.96	0.97	<.0001
Year of prescription	1.35	1.31	1.39	<.0001	1.43	1.39	1.46	<.0001

CKD, chronic kidney disease; CI, confidence interval; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; Unk/unspc, CKD stage unknown or unspecified.

Chapter 5.

Manuscript #3: Hypoglycemia Risk of SGLT2i or GLP-1RA versus Sulfonylureas among Medicare Insured Adults with CKD in the US

Hypoglycemia Risk of SGLT2i or GLP-1RA versus Sulfonylureas among Medicare Insured Adults with CKD in the US

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Abstract

Rationale & Objective: Information on safety issues of newer glucose-lowering medications from a large population perspective in chronic kidney disease (CKD) patients with type 2 diabetes is limited. Our study aimed to examine hypoglycemia risk associated with sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) versus second-generation sulfonylureas, in a general population of older patients with CKD and type 2 diabetes, across race, age, gender and socioeconomic subgroups.

Study Design: Retrospective cohort.

Setting & Participants: The 20% sample of Medicare fee-for-service claims, 2012-2018.

Exposures: Use of SGLT2i, GLP-1RA, or sulfonylurea.

Outcomes: Hypoglycemia events resulting in healthcare utilization.

Analytical Approach: Cox proportional hazard model evaluated the 90-day risk of hypoglycemia associated with SGLT2 inhibitors or GLP1 receptor agonists versus sulfonylureas.

Results: A total of 18,567 adults (≥18 years) with CKD and type 2 diabetes was included; 14.0% (n=2,528) had a prescription for a SGLT2i or GLP-1RA, and 86.0% (n=16,039) with a sulfonylurea. Compared with sulfonylureas, use of SGLT2i or GLP-1RA was significantly associated with a lower risk of hypoglycemic events (adjusted hazard ratio [aHR], 0.30; 95% confidence interval [CI], 0.14-0.65). Blacks had higher risk of developing hypoglycemia than Whites (aHR, 1.55; 95% CI, 1.07-2.26). Low-income subsidy (LIS) compared to no LIS was associated with higher risk of hypoglycemia events. The risk of hypoglycemia event also increased with higher comorbidity score (aHR, 1.05; 95% CI, 1.04-1.07).

Limitations: CKD and type 2 diabetes diagnosis, CKD stage and patient clinical status, were identified with diagnosis or procedure codes. There is potential for residual confounding with use of retrospective data.

Conclusions: Use of SGLT2i or GLP-1RA compared with sulfonylureas was associated with a decreased risk of hypoglycemia among patients with CKD and type 2 diabetes. Black race was not only associated with lower use of newer agents with demonstrated cardiovascular and kidney benefits and lower hypoglycemia risk, but also with a higher rate of hypoglycemia events as compared to Whites.

Introduction

An estimated 15% of US adults (≥18 years) (37 million people) have chronic kidney disease (CKD),[1] of which the leading cause is diabetes.[2] Type 2 diabetes management includes lifestyle modifications, psychosocial care, and pharmacologic approaches for glycemic control. However, glucose-lowering medications can lead to hypoglycemia, the most common adverse effect of diabetes treatment. When severe, it can cause coma and seizures.[3,4] A study based on continuous glucose monitoring system found that hypoglycemia (glucose <70 mg/dl) is associated with cardiac ischemia and symptoms.[5]

The kidneys play an important role in glucose hemostasis through kidney tubular glucose absorption and gluconeogenesis.[6] Hypoglycemia is increased in reduced kidney function. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, higher serum creatinine or higher urine albumin to creatinine ratio was associated with hypoglycemia requiring medical assistance.[7] A prospective observational study found that hypoglycemia is common among patients with CKD and type 2 diabetes; continuous glucose monitoring detected glucose ≤ 70 mg/dL in 76% (61/80) and glucose ≤ 60 mg/dL in 61% (49/80); 39% (31/80) experienced a prolonged hypoglycemic events (glucose ≤ 54 mg/dL for 120 consecutive minutes).[8]

Large clinical trials have shown benefits of newer glucose-lowering medications on cardiovascular and kidney outcomes in CKD patients with type 2 diabetes.[9–16] The risk of hypoglycemia was generally low with sodium–glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA) in these clinical trials. However, data from these clinical trials were based on selected patient populations. It is

important to assess whether the results of these clinical trials are applicable to CKD patients in routine clinical practice. There is limited information on safety issues of newer glucose-lowering medications from a large population perspective in CKD patients with type 2 diabetes. Additionally, there is no information on comparative hypoglycemia risk in different race, age, gender, or socioeconomic groups. Our study aimed to examine hypoglycemia risk associated with second-generation sulfonylureas versus SGLT2i or GLP-1RA, in a general population of older patients with CKD and type 2 diabetes, across race, age, gender and socioeconomic subgroups.

Methods

Data source

We used data from a 20% random sample of Medicare fee-for-service claims. To conduct this study, claims data files included patient demographic characteristics, health insurance enrollment, institutional (inpatient, outpatient, home health, skilled nursing facility), physician visits, and Part D characteristics files (including prescription events) from January 1, 2012 to December 31, 2018.

Study design and cohort selection

We conducted a retrospective cohort study design (**Figure 5.1**) in CKD patients with type 2 diabetes. First, we identified patients with CKD and type 2 diabetes from 2013 to 2018, and used International Classification of Disease, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) diagnosis codes provided by the United States Renal Data System (USRDS).[17] We excluded diagnoses related to type 1 diabetes (ICD-

9-CM: 250.X1/250.X3, X=0-9; ICD-10-CM: E10) to select patients more likely to have type 2 diabetes. Patients were considered as having type 2 diabetes if they had ≥ 1 diagnosis code from inpatient services, home health, or skilled nursing facilities, or ≥ 2 diagnosis codes from physician claims or outpatient services on different dates within 365 days. The same method was used to identify CKD patients. This method has been shown to increase sensitivity and specificity compared with using only one claim in patients with diabetes.[18] The first claim date was chosen for confirmed diagnosis. To establish CKD and type 2 diabetes diagnoses, the index date was defined by taking the claims date for the later of the two diagnoses. For example, if the diabetes date was June 15, 2013, and the CKD date was July 12, 2014. Then the CKD-type 2 diabetes diagnosis index date was July 12, 2014. Patients < 18 years old at the diagnosis index date were excluded.

Next, we identified patients who filled a first prescription of a sulfonylurea, SGLT2i or GLP-1RA from January 1, 2013 to September 30, 2018. The first prescription date of sulfonylurea, SGLT2i or GLP-1RA (**Table 5.1**) after the CKD-type 2 diabetes diagnosis index date was the prescription index date. We used a new user approach design. New users were patients without any glucose-lowering medication except use of metformin in the 180 days prior to the prescription index date. Additional inclusion criteria included continuous enrollment in Medicare Part A, Part B and Part D in one year before or on the prescription index date. Exclusion criteria included: 1) hypoglycemia events (**Supplementary Table S5.1**) in 180 days before or on the prescription index date, 2) organ transplant (**Supplementary Table S5.2**) in 180 days before or on then prescription index date), 3) indication of end-stage kidney disease (ESKD) on Centers for

Medicare & Medicaid Services (CMS) form 2728 or by diagnosis codes (ICD9, 5856/ICD10, N186) in the 180-day period before or on the prescription index date, 4) dose change in metformin during 30 days before or on the prescription index date, 5) dose change of non-glucose-lowering medications associated with hyper- or hypoglycemia (**Supplementary Table S5.3**) during 30 days before or on the prescription index date, 6) hospitalization not associated with hypoglycemia event during 90 days after or on the prescription index date.

Study covariates

Baseline covariates included patient demographics (age, gender, and race), low-income subsidy (LIS) status, CKD stage status, comorbid condition index score, and prescription medication use. The Medicare Part D program offers LIS benefits to enrollees with limited assets and income. The LIS provides full or partial waivers for out-of-pocket cost-sharing requirements including premiums, deductibles, and copayments. The LIS was used as a surrogate for lower socioeconomic status. To define comorbid conditions, we used a 1-year baseline period before the prescription index date. We identified non-glucose-lowering medications associated with hyper- or hypoglycemia in the 90-day period and other covariates in the 180-day period prior to the prescription index date. Comorbid conditions were identified based on the Elixhauser measure [19], and confirmed if at least one inpatient or two physician/outpatient services claims on different days were identified during the 1-year baseline period. A comorbid condition index score was calculated using van Walraven's method.[20] CKD stage was defined by stage-specific ICD-9/10-CM diagnosis codes (**Supplementary Table S5.4**). The code for the most

recent CKD stage (1 to 5) from outpatient or physician visit claims in the 180 days baseline period was used.

Study outcomes

Our outcome of interest was the first hypoglycemia event resulting in healthcare utilization within 90 days after the prescription index date. The event was identified by ICD-9/10-CM diagnosis codes (**Supplementary Table S5.1**) from hospital, observation stay, emergency department, urgent care, or clinic visits using Medicare inpatient, outpatient, or physician visits claim files.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). We described baseline characteristics across individuals initiating sulfonylureas, SGLT2i or GLP-1RA as count or percentage for categorical variables and mean for continuous variables. We used a Cox proportional hazard regression model to evaluate the 90-day risk of hypoglycemia associated with sulfonylureas versus SGLT2i or GLP-1RA. We selected a 90-day follow-up period consistent with published studies on hypoglycemia events.[21,22] Patients were followed from the prescription index date until the first hypoglycemia event, death, or censoring events. Censoring events included: 1) completion of a 90-day of follow-up, 2) study end, December 31, 2018, 3) end of health insurance coverage (Medicare Part A, Part B, or Part D), 4) development of ESKD, 5) medication refill gap of sulfonylureas, SGLT2i or GLP-1RA, metformin, or non-glucose-lowering medications that may be associated with hyper- or hypoglycemia during 90 days follow-up period from index date. More than 15 days gap between two prescription fill

dates was considered a refill gap, 6) dosing change of metformin or non-glucose-lowering medications (associated with hyper- or hypoglycemia) during 90 days follow-up period from the prescription index date, 7) having claims for new glucose-lowering medications or new non-glucose-lowering medications (associated with hyper- or hypoglycemia) during 90 days follow-up period from the prescription index date.

This study was approved by the Hennepin Healthcare Human Subjects Research Committee. A waiver of consent was issued due to data anonymity, use of secondary data and large population.

Results

The study cohort comprised 18,567 adults (≥18 years) with CKD and type 2 diabetes after applying study inclusion and exclusion criterion; 14.0% (n=2,528) had a prescription for a SGLT2i or GLP-1RA, and 86.0% (n=16,039) with a sulfonylurea. A CONSORT diagram for patient selection is provided in **Figure 5.2**. The mean age (SD) of all users was 72.9 (±10.0) years, 50.1% were women, 12.9% were black and 33.3% had the LIS. Sulfonylurea users had a higher mean Elixhauser comorbidity score than SGLT2i or GLP-1RA users. The proportion of patients with CKD stage 4-5 also was higher in sulfonylurea compared to SGLT2i or GLP-1RA users. Baseline characteristics in the overall cohort and by each treatment group are summarized in **Table 5.2**. The proportion of patients with new use of SGLT2i or GLP-1RA was lower among Black patients than Whites or Others (**Table 5.3**).

Hypoglycemic events in the treatment of SGLT2i or GLP-1RA vs. sulfonylurea were 0.3% and 1.2%, and the hypoglycemic events related to acute care was 43% and 76%, respectively. The cumulative probability of hypoglycemic events was shown in **Figure 5.3**. Adjusted risk for hypoglycemic events during the follow-up period is provided in **Table 5.4**. Compared with sulfonylureas, use of SGLT2i or GLP-1RA was significantly associated with a reduced risk of hypoglycemic events (adjusted hazard ratio [aHR], 0.30; 95% confidence interval [CI], 0.14-0.65) after adjustment for age, gender, race/ethnicity, CKD stage, comorbidity score, and baseline use of non-glucose-lowering medications associated with hyper- or hypoglycemia. Blacks had higher risk of developing hypoglycemia than Whites (aHR, 1.55; 95% CI, 1.07-2.26). Patients aged 75-84 years vs. 65-74 years had higher risk of hypoglycemia events (aHR, 1.45; 95% CI, 1.04-2.01). LIS compared to no LIS was associated with higher risk of hypoglycemia events. The risk of hypoglycemia event also increased with increased comorbidity score (aHR, 1.05; 95% CI, 1.04-1.07).

We conducted a sensitivity analysis to compare SGLT2i versus sulfonylurea use, and GLP-1RA versus sulfonylurea use, separately. Compared with sulfonylureas, SGLT2i agents were significantly associated with reduced risk of hypoglycemic events (aHR, 0.19; 95% CI, 0.14-0.65) after covariate adjustment. GLP-1RA use was marginally but not statistically significantly associated with reduced risk of hypoglycemic events (aHR, 0.47; 95% CI, 0.21-1.07, p =0.07).

Discussion

Among patients with CKD and type 2 diabetes, use of newer glucose-lowering medications (SGLT2i or GLP-1RA) compared with sulfonylureas was associated with decreased risk of hypoglycemia. These results add to limited observational evidence for the association of newer glucose-lowering medications compared with sulfonylureas with safety issues among patients with reduced kidney function. The association was independent of age, gender, race/ethnicity, baseline medication use, CKD stage condition and comorbidity conditions. We also showed that Black race, older age (75-84 years) and LIS status were associated with higher rate of developing hypoglycemia events.

Sulfonylureas are widely used as a diabetes treatment because they effectively lower blood glucose and hemoglobin A1c (HbA1c) and are available as generics. The second-generation agents (glyburide, glipizide, glimepiride) have largely replaced first generation drugs (chlorpropamide, tolazamide, tolbutamide) in the general population due to lower risk of hypoglycemia. Recently a meta-analysis of randomized controlled trials examined efficacy and safety of newer glucose-lowering medications. The study compared SGLT2i with sulfonylureas as second-line therapy in patients with type 2 diabetes inadequately controlled on metformin. The study included five trials involving 4,300 participants, and found that SGLT2i were associated with less hypoglycemia as add-on therapy to metformin (odds ratio [OR] 0.12; 95% CI [0.07, 0.21]) compared to sulfonylureas.[23]

While benefits of SGLT2i or GLP-1RA among patients with type 2 diabetes and CKD have been demonstrated, there is no evidence that sulfonylureas reduce either cardiovascular or kidney progression risk. The Kidney Disease: Improving Global Outcomes (KDIGO) provides more specific clinical guidelines for patients with CKD and

type 2 diabetes. In the 2021 KDIGO guideline, metformin and a SGLT2i are recommended as the first-line treatment choice for patients with CKD stage 3 or higher (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2). A SGLT2i is also recommended as second-line treatment to these patients. In patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin and a SGLT2i, or who are unable to use those medications, a GLP-1RA is recommended.[24]

Cost is an important factor that influences selection of newer medications such as a SGLT2i or GLP-1RA. Luo et al recently assessed annual out-of-pocket costs associated with commonly used SGLT2i or GLP-1RA across Part D plans. Median estimated annual out-of-pocket costs ranged from $1,211 (interquartile range [IQR], $1,167-$1,221) for ertugliflozin to $2,447 (IQR, $2,441-$2,464) for liraglutide with the standard Part D benefit design.[25] Medicare beneficiaries not eligible for LIS face very high out-of-pocket costs annually for SGLT2i or GLP-1RA. Moreover, canagliflozin, one of 200 drugs with the highest utilization by dual eligible patients having both Medicare and Medicaid benefits, was included on <75% of Part D plan formularies in 2019 and 2020.[26] High out-of-pocket costs and low rate of formulary inclusion in Part D plans likely limit access to these medications by many patients that may receive clinical benefits from these newer medications. A recent retrospective study using Medicare claims data showed that SGLT2i or GLP-1RA were only used in 3.3% and 6.1% in patients with CKD and type 2 diabetes, respectively, in 2016.[27] Another retrospective analysis using 2015-2019 data from Optum Clinformatics Data Mart also suggested that prescription of SGLT2i was low but increasing in commercially insured patients with type 2 diabetes. Furthermore,

the study showed that there were racial/ethnic, gender, and socioeconomic disparities in receipt of SGLT2i therapy. SGLT2i use was lower in Black patients.[28] We observed that Black and older patients with CKD were less likely to receive these newer agents, were more likely to receive sulfonylureas, which have higher risk for hypoglycemia, and were also at significantly higher risk of developing hypoglycemia after adjustment for other medications and covariates.

Health disparities in Black patients with diabetes and CKD have been well demonstrated. A cohort study with 4,251 participants found that the chance of developing diabetes was significantly higher for Black than for White adults (about 66 more cases of diabetes per 1,000 people).[29] A large cohort study in multiethnic patients free of cardiovascular disease and with eGFR >60 ml/min per 1.73 m^2 at baseline found that kidney function decline varied significantly by race/ethnicity. Blacks had a significantly higher rate of kidney function decline than whites (0.31 ml/min per 1.73 m^2/year faster on average, $p = 0.001$) after adjusting for multiple potential confounders.[30] USRDS 2020 annual data reported that the adjusted prevalence of ESKD was 3.4 times higher in Blacks than Whites in 2018.[17] The results of our study highlight the importance of developing policies to address these disparities in Black patients at higher risk for development of CKD and ESKD, and to mitigate health disparities due to financial burden.

Our study has several strengths. We focused on health disparities regarding hypoglycemia risk in a large population of older CKD patients with type 2 diabetes filling prescriptions for newer glucose-lowering medications. Additionally, SGLT2i or GLP-1RA clinical trials have included CKD patients, but the majority were conducted in

patients with eGFR ≥ 30 ml/min per 1.73 m^2. There is limited data on hypoglycemia risk of these agents among patients with type 2 diabetes and CKD stages 4-5. Also, we used a new user design, which reduces the risk of selection bias that can occur when patients have previously been exposed to these drug classes. To capture more potential confounding effects, we adjusted for the effect of non-glucose-lowering medications associated with hyper- or hypoglycemia and censored follow-up at medication change, refill gap, and dosing change. Compared with small data sources, we used the large Medicare claims database to capture comprehensive longitudinal information on patient demographics, inpatient and outpatient diagnoses and procedures, and prescriptions. We used actual medication claims dispensing records rather than other data sources that measure prescribing patterns not patient use.

The study has several limitations. CKD and type 2 diabetes diagnosis, CKD stage and patient clinical status, were identified with diagnosis or procedure codes because laboratory values were not available from the data sources. We may have underestimated the overall incidence of hypoglycemia by excluding patients with a history of hypoglycemia events before the prescription index date. There is potential for residual confounding with use of retrospective data. We adjusted our analysis by important risk factors (age, kidney function, and other chronic conditions), however we could not adjust for all potential confounders, especially lifestyle factors. Our analysis cohort consisted of CKD patients enrolled in Medicare Part D coverage; utilization patterns may differ for patients enrolled in non-Part D prescription plans or Medicare Advantage plans or other types of health insurance. The Medicare data set does not include patients aged younger than 65 years, except for those with disabilities. Generalizability to other population

should be considered carefully. We excluded ESKD patients, so our results can't be extrapolated to this population. The LIS was used as surrogate for socioeconomic status; other socioeconomic data was not available. Finally, information provided in Medicare Part D claims is based on dispensed prescription which reflect prescription acquisition patterns and does not reflect patient consumption behavior.

Conclusions

Among patients with CKD and type 2 diabetes, use of SGLT2i or GLP-1RA compared with sulfonylureas was associated with a decreased risk of hypoglycemia. Our results provide real-world evidence on the association of SGLT2i or GLP-1RA use with the risk of hypoglycemia. Importantly, our results demonstrate that Black race was not only associated with lower use of newer agents with demonstrated cardiovascular and kidney benefits and lower hypoglycemia risk, but also with a higher rate of hypoglycemia events as compared to Whites. These results are a call for action for new policies that eliminate disparities in access and use of these newer agents in Blacks and those with lower socioeconomic status.

Article Information Section

Authors' Contributions

Research idea and study design: JZ, AC, WSP; data acquisition: JZ, EW, WSP; data analysis/interpretation: JZ, EW, WSP; statistical analysis: JZ, EW, WSP; supervision or mentorship: WSP. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 5.1. Description of glucose-lowering medications prescriptions evaluated in the study

Class	Medication	FDA approval date
Sulfonylureas (2nd generation)	glipizide	2002
	glyburide	2002
	glimepiride	1999
SGLT2i	canagliflozin	2013
	dapagliflozin	2014
	empagliflozin	2014
	ertugliflozin	2017
GLP-1RA	albiglutide	2014
	dulaglutide	2014
	exenatide	2005
	exenatide extended-release	2012
	liraglutide	2010
	lixisenatide	2016
	semaglutide	2017

FDA, the Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Table 5.2. Baseline Characteristics of CKD patients aged ≥ 18 years with type 2 diabetes, Medicare 20% CKD claims, 2012-218

Baseline characteristics	Overall cohort	SGLT2i/GLP-1RA	Sulfonylurea
Total (n)	18567	2528	16039
Age			
mean (std), year	72.9 (10.0)	68.8 (9.9)	73.5 (9.9)
Age category, years			
18-64 y	2594 (14.0%)	551 (21.8%)	2043 (12.7%)
65-74 y	7929 (42.7%)	1334 (52.8%)	6595 (41.1%)
75-84 y	5865 (31.6%)	549 (21.7%)	5316 (33.1%)
>= 85 y	2179 (11.7%)	94 (3.7%)	2085 (13.0%)
Sex			
Male	9262 (49.9%)	1223 (48.4%)	8039 (50.1%)
Female	9305 (50.1%)	1305 (51.6%)	8000 (49.9%)
Race/Ethnicity			
White	14598 (78.6%)	2069 (81.8%)	12529 (78.1%)
Black	2396 (12.9%)	244 (9.7%)	2152 (13.4%)
Other/unknown	1573 (8.5%)	215 (8.5%)	1358 (8.5%)
Low income subsidy (LIS) status			
Non-LIS	12384 (66.7%)	1721 (68.1%)	10663 (66.5%)
LIS	6183 (33.3%)	807 (31.9%)	5376 (33.5%)
CKD stage			
1/2	1832 (9.9%)	312 (12.3%)	1520 (9.5%)
3	6474 (34.9%)	697 (27.6%)	5777 (36.0%)
4/5	738 (4.0%)	37 (1.5%)	701 (4.4%)
Unk/Unspc	9523 (51.3%)	1482 (58.6%)	8041 (50.1%)
Metformin	11241 (60.5%)	1691 (66.9%)	9550 (59.5%)
Non-glucose-lowering medications associated with hyperglycemia	11164 (60.1%)	1599 (63.3%)	9565 (59.6%)
Statins	9862 (53.1%)	1424 (56.3%)	8438 (52.6%)

Tricyclic antidepressants	659 (3.5%)	137 (5.4%)	522 (3.3%)
Corticosteroids	2246 (12.1%)	287 (11.4%)	1959 (12.2%)
Non-glucose-lowering medications associated with hypoglycemia	4884 (26.3%)	743 (29.4%)	4141 (25.8%)
Antibiotics	1890 (10.2%)	248 (9.8%)	1642 (10.2%)
SSRIs	3094 (16.7%)	514 (20.3%)	2580 (16.1%)
MAOIs	*	*	*
Antihypertensives (Noncardioselective)	431 (2.3%)	56 (2.2%)	375 (2.3%)
ELIXHAUSER Comorbidity Index Score			
mean (std)	8.5 (8.9)	6.1 (8.0)	8.8 (9.0)

CKD, chronic kidney disease; std, standard deviation; GLP-1RA, glucagon-like peptide-1 receptor agonists; MAOI, Monoamine oxidase inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SSRI, Serotonin selective reuptake inhibitors; Unk/unspc, CKD stage unknown or unspecified.

Note: * refers to counts of 10 or fewer patients.

Table 5.3. Differences in new use of SGLT2i/GLP-1RA versus sulfonylureas across age, sex, race/ethnicity and low income subsidy groups in patients with CKD and type 2 diabetes

Baseline characteristics	**Overall cohort**	**SGLT2i/GLP-1RA**		**Sulfonylurea**	
Total (n)	18,567	2,528		16,039	
Age category, years					
18-64 y	2,594	551	21.2%	2,043	78.8%
65-74 y	7,929	1,334	16.8%	6,595	83.2%
75-84 y	5,865	549	9.4%	5,316	90.6%
>= 85 y	2,179	94	4.3%	2,085	95.7%
Sex					
Male	9,262	1,223	13.2%	8,039	86.8%
Female	9,305	1,305	14.0%	8,000	86.0%
Race/Ethnicity					
White	14,598	2,069	14.2%	12,529	85.8%
Black	2,396	244	10.2%	2,152	89.8%
Other/unkown	1,573	215	13.7%	1,358	86.3%
Low income subsidy (LIS) status					
Non-LIS	12,384	1,721	13.9%	10,663	86.1%
LIS	6,183	807	13.1%	5,376	86.9%

CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Table 5.4. Hazard ratios for risk of hypoglycemia in CKD patients aged ≥ 18 years with type 2 diabetes

Analysis	Hazard ratio	95% CI		p-value
Glucose-lowering medication				
Sulfonylurea	Ref.			
SGLT2i/GLP-1RA	0.30	0.14	0.65	0.002
Age category, years				
18-64 y	0.93	0.57	1.52	0.779
65-74 y	Ref.			
75-84 y	1.45	1.04	2.01	0.027
>= 85 y	1.02	0.64	1.61	0.948
Sex				
Male	0.80	0.60	1.06	0.118
Female	Ref.			
Race/Ethnicity				
White	Ref.			
Black	1.55	1.07	2.26	0.022
Other/unknown	1.17	0.70	1.95	0.541
Low income subsidy (LIS)				
Non-LIS	Ref.			
LIS	1.56	1.14	2.14	0.005
CKD stage				
1/2	1.02	0.60	1.73	0.956
3	Ref.			
4/5	1.68	0.97	2.89	0.064
Unk/Unspc	1.15	0.84	1.57	0.377
ELIXHAUSER Comorbidity Index Score	1.05	1.04	1.07	<.0001
Metformin				
No	Ref.			
Yes	0.91	0.68	1.21	0.507
Non-glucose-lowering medications associated with hyperglycemia				
No	Ref.			
Yes	0.94	0.71	1.25	0.686
Non-glucose-lowering medications associated with hypoglycemia				
No	Ref.			
Yes	1.12	0.81	1.55	0.488

CKD, chronic kidney disease; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; Unk/unspc, CKD stage unknown or unspecified.

Figure Legends

Figure 5.1. Retrospective cohort study design. CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors. *Note*: no prescription claims for any glucose-lowering medications (except metformin) were allowed during baseline period. * Non-glucose-lowering medications associated with hyper- or hypoglycemia were identified in the 90-day period and other covariates were identified in the 180-day period prior to the prescription index date; ** Comorbid conditions were identified during the 1-year baseline period; [a] The earliest date in database; [b] The earliest possible starting time; [c] The latest possible starting time; [d] The latest date in database; [#] Until a hypoglycemia or censoring event.

Figure 5.2. Consort diagram for patient selection. CKD, chronic kidney disease; CMS, Centers for Medicare & Medicaid Services; ESKD, end stage kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Figure 5.3. The Nelson-Aalen estimate 90-day cumulative incidence of hypoglycemic events. GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Figure 5.1.

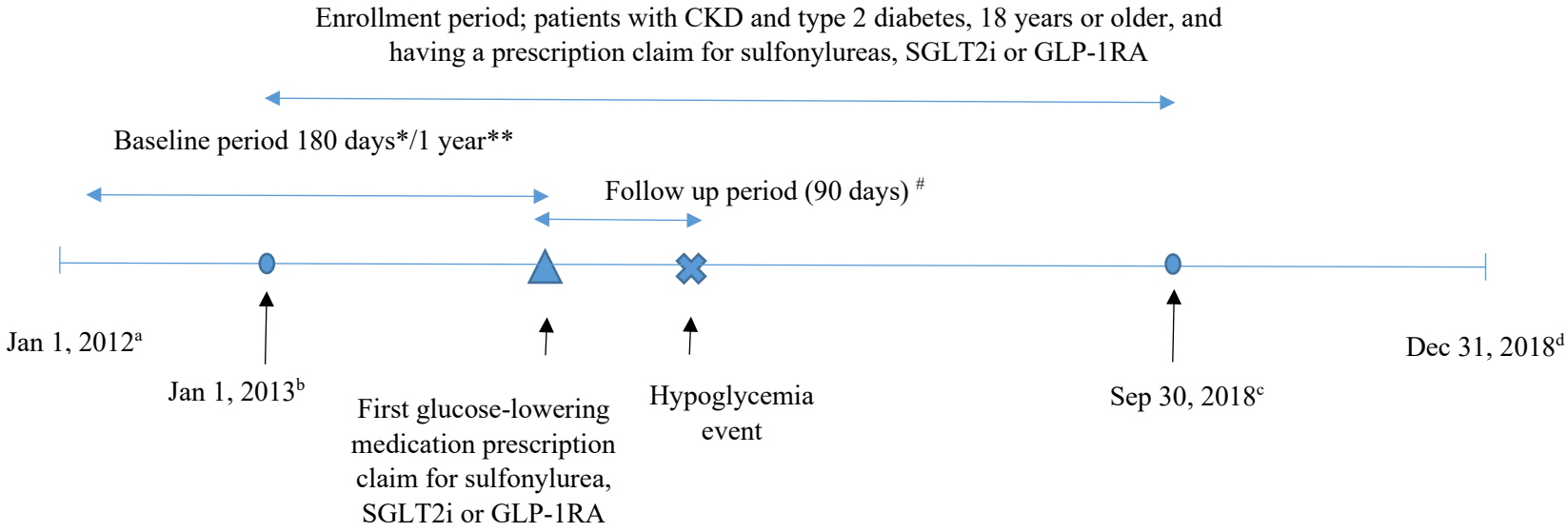
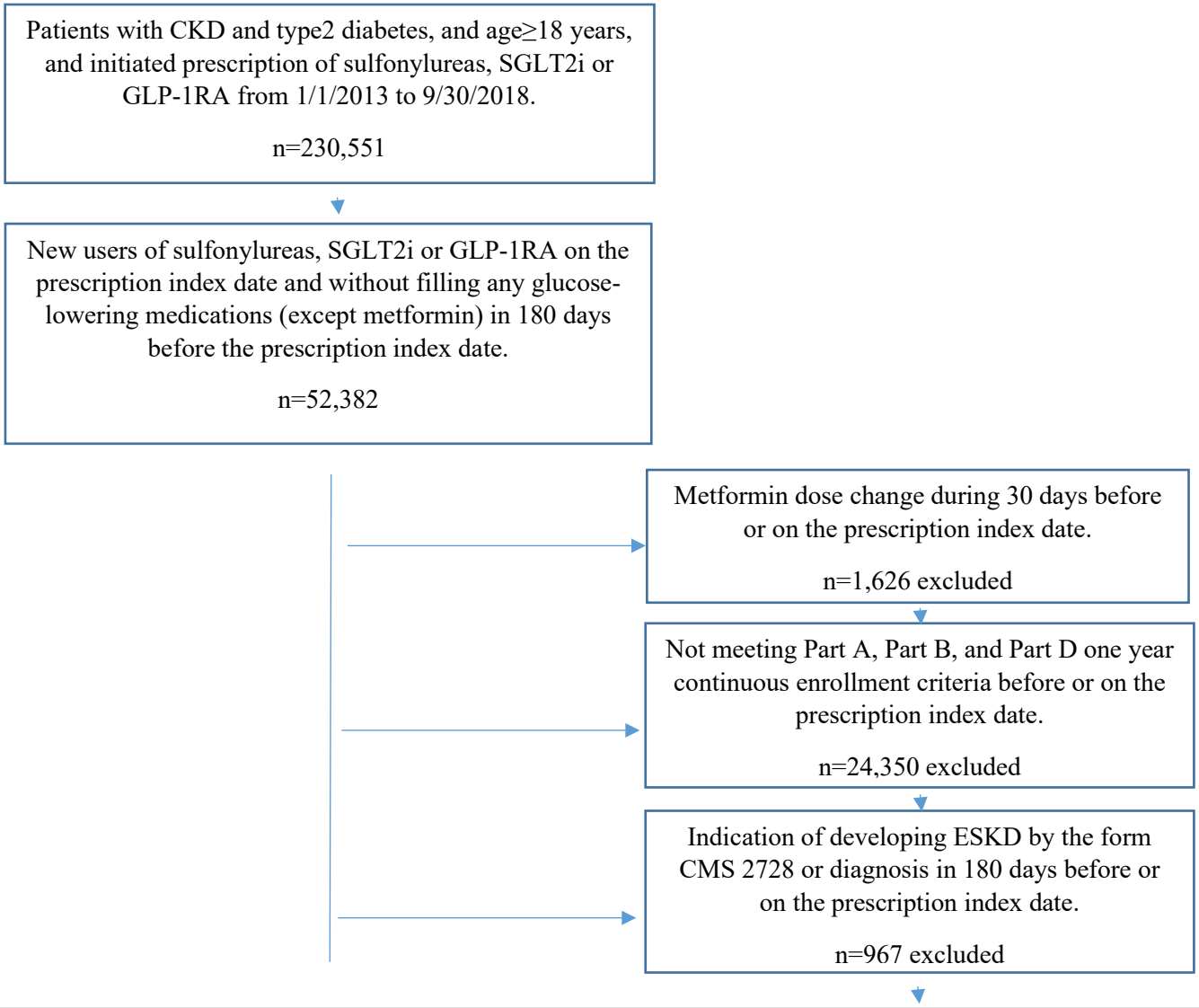

Enrollment period; patients with CKD and type 2 diabetes, 18 years or older, and having a prescription claim for sulfonylureas, SGLT2i or GLP-1RA
Baseline period 180 days*/1 year**
Follow up period (90 days) #
Jan 1, 2012a
Jan 1, 2013b
First glucose-lowering medication prescription claim for sulfonylurea, SGLT2i or GLP-1RA
Hypoglycemia event
Sep 30, 2018c
Dec 31, 2018d

Figure 5.2.


Patients with CKD and type2 diabetes, and age≥18 years, and initiated prescription of sulfonylureas, SGLT2i or GLP-1RA from 1/1/2013 to 9/30/2018.
n=230,551
New users of sulfonylureas, SGLT2i or GLP-1RA on the prescription index date and without filling any glucose-lowering medications (except metformin) in 180 days before the prescription index date.
n=52,382
Metformin dose change during 30 days before or on the prescription index date.
n=1,626 excluded
Not meeting Part A, Part B, and Part D one year continuous enrollment criteria before or on the prescription index date.
n=24,350 excluded
Indication of developing ESKD by the form CMS 2728 or diagnosis in 180 days before or on the prescription index date.
n=967 excluded

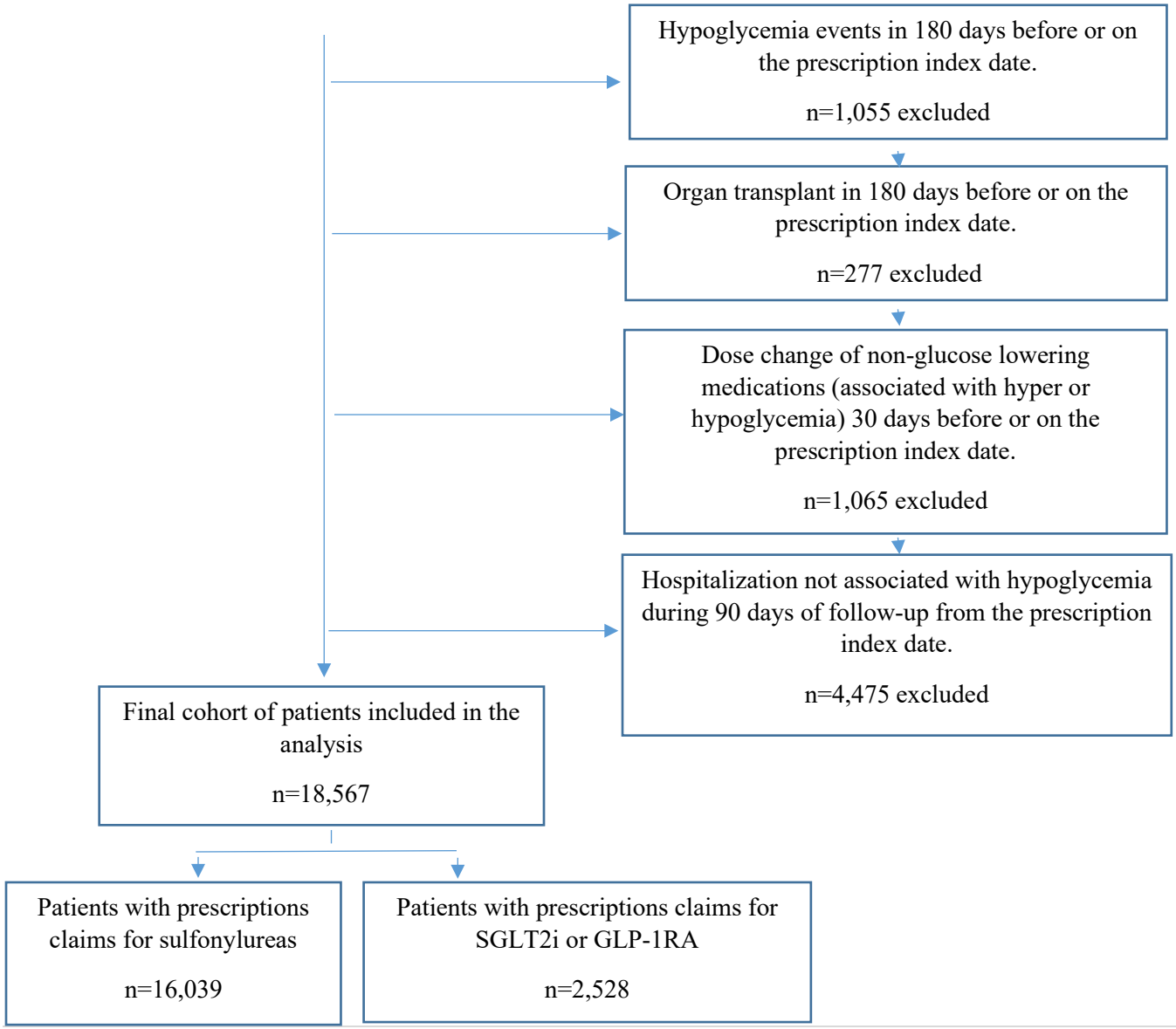
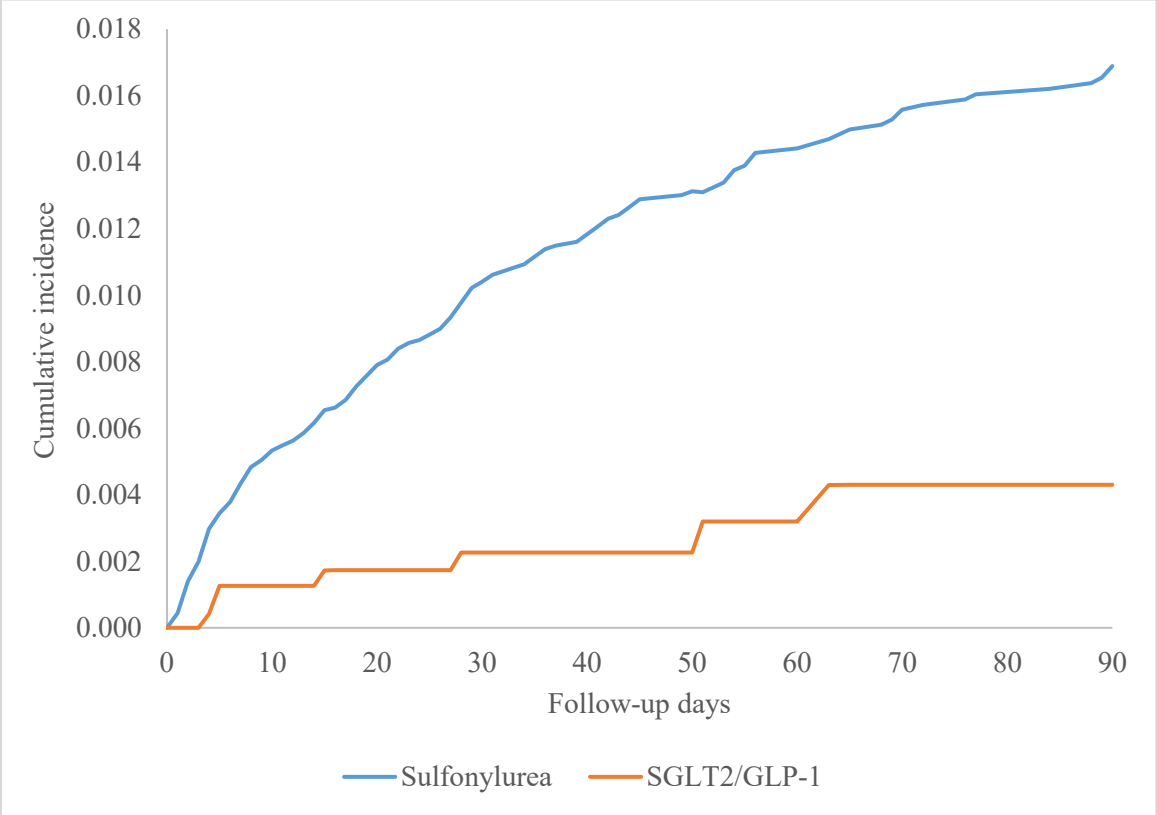

Hypoglycemia events in 180 days before or on the prescription index date.
n=1,055 excluded
Organ transplant in 180 days before or on the prescription index date.
n=277 excluded
Dose change of non-glucose lowering medications (associated with hyper or hypoglycemia) 30 days before or on the prescription index date.
n=1,065 excluded
Hospitalization not associated with hypoglycemia during 90 days of follow-up from the prescription index date.
n=4,475 excluded
Final cohort of patients included in the analysis
n=18,567
Patients with prescriptions claims for sulfonylureas
n=16,039
Patients with prescriptions claims for SGLT2i or GLP-1RA
n=2,528

Figure 5.3.


0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
Cumulative incidence
0
10
20
30
40
50
60
70
80
90
Follow-up days
Sulfonylurea
SGLT2/GLP-1

Supplementary Material

Table S5.1. ICD-9/10-CM diagnosis codes for hypoglycemia

Table S5.2. ICD-9/10 and CPT codes for solid organ transplants

Table S5.3. Non-glucose-lowering medications which are associated with hyperglycemia or hypoglycemia

Table S5.4. Chronic kidney disease stage-specific ICD-9/10-CM diagnosis codes

Supplementary Table S5.1. ICD-9/10-CM diagnosis codes for hypoglycemia

ICD-9-CM [a]	251.0; 251.1; 251.2; 250.8 and without any of co-diagnosis: 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.xx, 709.3, 730.0–730.2, or 731.8.
ICD-10-CM [b]	E160; E161; E162; E1164; E1364; E1064; E0864.

ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revision, Clinical Modification diagnosis codes.

Source: [a] Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord.* 2008;8:4. [b] Dugan J, Shubrook J. International Classification of Diseases, 10th Revision, Coding for Diabetes. *Clin Diabetes*. 2017;35(4):232-238.

Supplementary Table S5.2. ICD-9/10 and CPT codes for solid organ transplants

ICD-9 [a]	Diagnosis	Kidney: 996.81; V42.0; Heart: 996.83; V42.1; Lung: 996.84; V42.6; Liver: 996.82; V42.7.
	Procedure	Kidney: 5561; 5569 Heart: 3751; Lung: 3350; 3351;3352; Liver: 5051; 5059.
ICD-10 [b]	Diagnosis	Kidney: T86.10; T86.11; T86.12; T86.13; T8619; Z94.0; Heart: T86.20; T86.21; T86.22; T86.23; T86.290; T86.298; Z94.1; Lung: T86.810; T86.811; T86.812; T86.818; T86.819; Z94.2; Liver: T86.40; T86.41; T86.42; T86.43; T86.49; Z94.4.
	Procedure	Kidney: 0TY00Z0; 0TY00Z1; 0TY00Z2; 0TY10Z0; 0TY10Z1; 0TY10Z2; Heart: 02YA0Z0; 02YA0Z1; 02YA0Z2; Lung: 0BYK0Z0; 0BYK0Z1; 0BYK0Z2; 0BYL0Z0; 0BYL0Z1; 0BYL0Z2; 0BYC0Z0; 0BYC0Z1; 0BYC0Z2; 0BYD0Z0; 0BYD0Z1; 0BYD0Z2; 0BYF0Z0; 0BYF0Z1; 0BYF0Z2; 0BYG0Z0; 0BYG0Z1; 0BYG0Z2; 0BYH0Z0; 0BYH0Z1; 0BYH0Z2; 0BYJ0Z0; 0BYJ0Z1; 0BYJ0Z2; 0BYK0Z0; 0BYK0Z1; 0BYK0Z2; 0BYL0Z0; 0BYL0Z1; 0BYL0Z2; 0BYM0Z0; 0BYM0Z1; 0BYM0Z2; Liver: 0FY00Z0; 0FY00Z1; 0FY00Z2.
CPT [a]		Kidney: 50360; 50365; Heart: 33945; Lung: 00580; 32854; 32853; 32852; 32851; 33935; Liver: 47135.

ICD-9/10, International Classification of Disease, Ninth/Tenth Revision.

Source: [a] Sigel K, Veluswamy R, Krauskopf K, et al. Lung Cancer Prognosis in Elderly Solid Organ Transplant Recipients. *Transplantation.* 2015;99(10):2181-2189. [b] HIPAASPACE. https://www.hipaaspace.com/medical_billing/crosswalk.services/icd-9.to.icd-10.mappi

Supplementary Table S5.3. Non-glucose-lowering medications which are associated with hyperglycemia or hypoglycemia

Category	Medication Class	Mechanism of Glucose Lowering Effects	Study	Design	Results/Summary	Selected Medications in our study
Antihypertensive	Non-cardioselective beta blocker/ cardioselective beta blocker	Hypoglycemia; inhibit hepatic glucose production and glycogenolysis; attenuates signs and symptoms.	Shorr RI et al. (1997)	Retrospective cohort study, n=13,559	Non-cardioselective ß-blockers were associated with the highest rate of hypoglycemia, but none of the findings was statistically significant.	levobunolol, metipranolol, nadolol, propranolol, sotalol, timolol.
			Mays et al. (2011)	Systematic review	Non-cardioselective β-blockers such as propranolol are more likely to cause hypoglycemia than cardio selective ones such as atenolol and metoprolol.	
	Angiotensin-converting enzyme (ACE) inhibitors	Hypoglycemia; increases insulin sensitivity	Mays et al. (2011)	Systematic review	Small studies, and the data remain controversial.	
Lipid lowering medications	Statins	Hyperglycemia; Statins may lead to increase of insulin-resistance.	Kim et al. (2018)	Retrospective cohort of non-diabetic individuals, n= 379,865	Use of atorvastatin, rosuvastatin, pitavastatin, and simvastatin were significantly associated with increase of the	atorvastatin, rosuvastatin, simvastatin.

					changes in fasting glucose. The effects of pravastatin, lovastatin, and fluvastatin were not significant.	
			L. Maria Belalcazar et al. (2009)	Systematic review	Simvastatin and atorvastatin, but not pravastatin, have been shown to decrease insulin secretion in Beta cells./The JUPITER trial reported that rosuvastatin therapy was associated with a mild but significant increase in the identification of new-onset diabetes.	
Antidepressants	Monoamine oxidase inhibitors (MAOIs)	Hypoglycemia	Goodnick et al. (1995)	Systematic review	MAOI use is related to the possible severity of the induced hypoglycemia, induced weight gain, and required diets.	isocarboxazid, phenelzine, selegiline, tranylcypromine.
			Barnard et al.(2013)	Systematic review	MAOIs were associated with improved glycemic control.	
	Serotonin selective reuptake inhibitors (SSRIs)	Hypoglycemia	Goodnick et al. (1995)	Systematic review	SSRIs may be hypoglycemic (causing as much as a 30% decrease in fasting plasma glucose).	citalopram, escitalopram, fluoxetine, paroxetine, sertraline.
			Barnard et al.(2013)	Systematic review	SSRIs were associated with improved glycemic	

					control./Serotonergic antidepressants, such as fluoxetine, reduced hyperglycemia, normalized glucose homeostasis, and increased insulin sensitivity.	
	Tricyclic antidepressants	Hyperglycemia	Goodnick et al. (1995)	Systematic review	The tricyclic antidepressants may lead to hyperglycemia, to an increase in carbohydrate craving (from 86% to 200%), and impaired memory.	amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine.
	Serotonin-norepinephrine reuptake inhibitors (SNRI)	Dual-mechanism	Barnard et al.(2013)	Systematic review	Dual-mechanism antidepressants, such as duloxetine and venlafaxine, did not appear to disrupt glucose homeostasis dynamics.	
Antibiotics/ quinolones	Ciprofloxacin	Hypoglycemia	Berhe et al. (2019)	Cases report (35 cases)	This study suggests that ciprofloxacin can cause hypoglycemia even in nondiabetic patients.	ciprofloxacin, levofloxacin, moxifloxacin.
			Parekh et al. (2014)	Retrospective cohort study of Texas Medicare claims	Ciprofloxacin (OR, 1.62 [95% CI, 1.33–1.97]) were associated with higher rates of hypoglycemia.	

	Levofloxacin	Hypoglycemia	Parekh et al. (2014)	Retrospective cohort study of Texas Medicare claims	Levofloxacin (OR, 2.60 [95% CI, 2.18–3.10]) were associated with higher rates of hypoglycemia.	
	Moxifloxacin	Hypoglycemia	Parekh et al. (2014)	Retrospective cohort study of Texas Medicare claims	Moxifloxacin were not significantly associated with hypoglycemia.	
Corticosteroids		Hyperglycemia				betamethasone budesonide dexamethasone cortisone methylprednisolone prednisolone prednisone

CI, confidence interval.

Reference:

Shorr RI, Ray WA, Daugherty JR, Griffin MR. Antihypertensives and the Risk of Serious Hypoglycemia in Older Persons Using Insulin or Sulfonylureas. JAMA. 1997;278 (1):40–43. https://jamanetwork.com/journals/jama/article-abstract/417273

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Supplementary Table S5.4. Chronic kidney disease stage-specific ICD-9/10-CM diagnosis codes

CKD stage	ICD-9-CM diagnosis codes	ICD-10-CM diagnosis codes	GFR
Stage 1	585.1	N18.1	≥ 90 ml/min/1.73 m^2
Stage 2	585.2	N18.2	60-89 ml/min/1.73 m^2
Stage 3	585.3	N18.3	30-59 ml/min/1.73 m^2
Stage 4	585.4	N18.4	15-29 ml/min/1.73 m^2
Stage 5	585.5	N18.5	<15 ml/min/1.73 m^2

GFR, glomerular filtration rate; ICD-9/10-CM, International Classification of Disease, Ninth/Tenth Revisions, Clinical Modification diagnosis codes.

Source: United States Renal Data System (USRDS). 2020 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

Chapter 6. Summary

6.1 Summary of findings

Selecting effective and safe glucose-lowering medications for chronic kidney disease (CKD) patients is challenging. Pharmacokinetics of various glucose-lowering medications are altered and some medications lose effectiveness as kidney function declines, necessitating dosage adjustments or discontinuation. Findings from the general population in use of glucose-lowering medications are commonly extrapolated. But few studies have examined utilization of glucose-lowering medications and safety issues in real-world populations of CKD patients.

Study 1 identified that use of metformin and newer glucose-lowering medication classes (dipeptidyl peptidase 4 inhibitors [DPP-4i], glucagon-like peptide-1 receptor agonists [GLP-1RA], sodium-glucose cotransporter 2 inhibitors [SGLT2i]) in CKD patients showed statistically significant upward trends. However, prescription of these newer glucose-lowering medications was low in 2016. GLP-1RA and SGLT2i were only used in 6.1% and 3.3% in patients with CKD and type 2 diabetes, respectively, in 2016.

Study 2 identified disparities in use of SGLT2i and GLP-1RA in CKD patients. Black race was associated with a significantly lower rate of SGLT2i and GLP-1RA use, while Hispanic ethnicity and Asian race were associated with a significantly lower rate of GLP-1RA use compared to Whites. Compared with CKD stage 3 patients, CKD stage 4-5 patients were associated with lower odds of starting SGLT2i or GLP-1RA than sulfonylureas. Patients with cardiovascular disease or hyperlipidemia were more likely to start SGLT2i or GLP-1RA.

Study 3 showed that use of newer glucose-lowering medications (SGLT2i or GLP-1RA) when compared with sulfonylureas use was associated with decreased risk of hypoglycemia resulting in healthcare utilization. These results add to limited observational evidence for the association of newer glucose-lowering medications compared with sulfonylureas with safety issues among patients with reduced kidney function. Black and older patients with CKD were less likely to receive these newer agents, were more likely to receive sulfonylureas, which have higher risk for hypoglycemia, and were also at significantly higher risk of developing hypoglycemia after adjustment for other medications and covariates.

6.2 Future research

Our study results can help providers understand current utilization patterns of glucose-lowering medications in CKD patients. Further investigations are needed to examine the impact of newly published clinical trial results on utilization patterns of glucose-lowering medications in CKD patients, especially patients with estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m^2. With proven cardiovascular and kidney benefits, the Kidney Disease: Improving Global Outcomes (KDIGO) recommendation on use of SGLT2i in CKD patients with eGFR ≥30 ml/min/1.73 m^2 is strong. It is important to examine changing utilization pattern of glucose-lowering medications due to the new updated guideline. Further examinations of real-world data are needed to confirm healthcare outcomes related to safety and effectiveness of glucose-lowering medications in CKD patients.

We identified disparities in use of SGLT2i and GLP-1RA. Importantly, our results demonstrate that Black race and older patients were not only associated with lower use of newer agents with demonstrated cardiovascular and kidney benefits and lower hypoglycemia risk, but also with a higher rate of hypoglycemia events. Future studies are needed to understand the barriers for prescription of these new medications, which have been demonstrated to improve kidney and cardiovascular outcomes across race groups and in older patients with CKD and type 2 diabetes.

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