

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



Julie Z. Zhao, Eric D. Weinhandl, Angeline M. Carlson, and Wendy L. St. Peter

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

**Study Design:** Retrospective cohort study.

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

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

**Outcomes:** Trends in use 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 low-income subsidy 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 analogue 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 low-income subsidy than among non-low-income subsidy patients. Combination therapy was less common as CKD stage increased.

**Limitations:** Patients with CKD and type 2 diabetes and the CKD stages were identified with diagnosis codes and could not be verified through medical record review. Our results may not be generalizable to younger patients with CKD with type 2 diabetes.

**Conclusions:** Use of metformin and newer glucose-lowering medication classes is increasing in patients with CKD with type 2 diabetes. We anticipate that percentages of patients with CKD using these newer agents will increase.

### Visual Abstract included

Complete author and article information provided before references.

Correspondence to J.Z. Zhao (zhaox086@umn.edu)

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Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD).<sup>1</sup> According to National Health and Nutrition Examination

agonists, bile acid sequestrants, dopamine 2 agonists, amylin mimetics, and insulins.<sup>3</sup>

Evidence supporting their effectiveness in patients with CKD is increasing. For example, Arjona Ferreira et al<sup>4</sup> compared sitagliptin with glipizide regarding glucose lowering in patients with moderate to severe CKD and demonstrated the efficacy of sitagliptin in a randomized clinical trial. 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.<sup>5,6</sup>

Information on the use of glucose-lowering medications in patients with CKD is limited. Our study aimed to: (1) update trends in the use of individual glucose-lowering medications and distinct therapeutic classes in patients with CKD with diabetes, (2) determine which monotherapies and combination therapies were commonly prescribed for patients with CKD with diabetes, and (3) examine patterns of glucose-lowering medication use 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 US Renal Data

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Survey data, the prevalence of CKD (stages 3 and 4) among US adults with diagnosed diabetes was 24.5% (27.1%-22.1%), and 4.9% (6.1%-4.1%) among those without diabetes in 2011 to 2014.<sup>2</sup>

In addition to lifestyle modifications and psychosocial care, diabetes treatment includes pharmacologic approaches for glycemic control. Selecting effective and safe glucose-lowering medications for patients with CKD 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 (Table S1): biguanides, sulfonylureas, thiazolidinediones (TZDs), 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

**PLAIN-LANGUAGE SUMMARY**

Recent data on the use of glucose-lowering medications in patients with chronic kidney disease (CKD) are lacking. We used Medicare 5% random sample data from 2007 to 2016 to examine trends in the use of individual glucose-lowering medications and distinct therapeutic classes in patients with CKD with type 2 diabetes. To test overall trends in glucose-lowering medication classes, we adjusted for age, sex, race/ethnicity, CKD stage, and low-income subsidy status. It is important to understand these trends and why they are occurring, especially given emerging data showing that sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists can reduce albuminuria and slow CKD progression.

System.<sup>7</sup> We used 2007 to 2016 data, including patient enrollment and demographic characteristic information and institutional Part A, noninstitutional 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 Diseases, Ninth/Tenth Revision, Clinical Modification* diagnosis codes.<sup>8</sup> Eligible patients had 1 or more codes from inpatient services, home health, or skilled nursing facilities or 2 or more codes from physician claims or outpatient services on different claim dates within each cohort year for CKD (Table S2) and for type 2 diabetes (Table S3). Use of 2 outpatient claims has been shown to increase sensitivity and specificity compared with using only 1 claim for diabetes.<sup>9</sup> Eligible patients who met the following criteria were included in the study: (1) had CKD and type 2 diabetes, 18 years or older, 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 *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* diagnosis codes (Table S4). If multiple claims related to different CKD stages appeared in a cohort year, the most frequent stage (1-5) within the calendar year was used. If the same number of claims appeared for 2 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

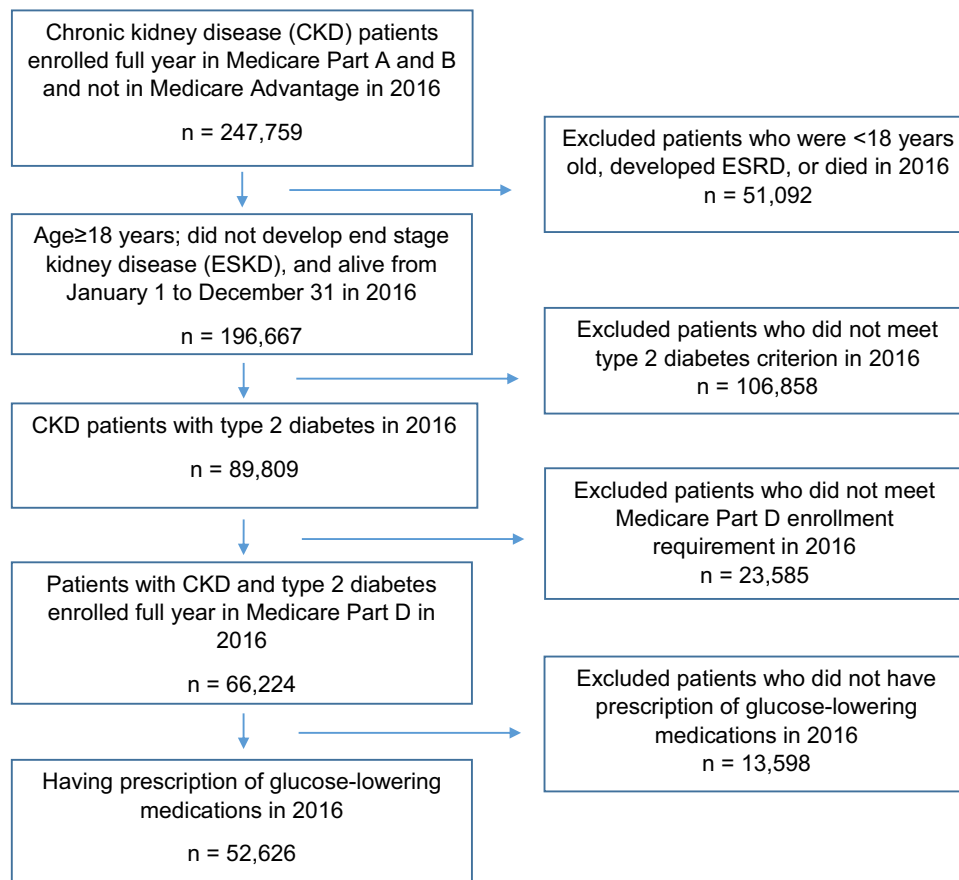
**Table 1.** Characteristics of CKD Patients 18 Years or Older With Type 2 Diabetes Using Glucose-Lowering Medication, Medicare 5% CKD Claims, in 2007, 2012, and 2016

	2007	2012	2016
Total	19,257	31,888	52,626
Age, y	73.0 ± 11.0	73.9 ± 10.7	73.7 ± 10.2
Age category, y			
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%)
Low-income subsidy status			
Non-low-income subsidy	7,891 (41.0%)	14,756 (46.3%)	31,101 (59.1%)
Low-income subsidy	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%)
Unknown/unspecified	10,148 (52.7%)	11,357 (35.6%)	16,687 (31.7%)

NOTE: Values for age as a continuous variable are given as mean ± standard deviation.

Abbreviation: CKD, chronic kidney disease.

(ADA) 2018 guideline “Pharmacologic Approaches to Glycemic Treatment” to identify medications from Part D claims data.<sup>3</sup> Medication use was defined by at least



**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram for patient selection in 2016. Abbreviations: CKD, chronic kidney disease; ESK(R)D, end-stage kidney (renal) disease.

1 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 1 glucose-lowering medication class overlapping for at least 2 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 status were used. To account for repeated observations (calendar years) per patient, generalized estimating equations 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).

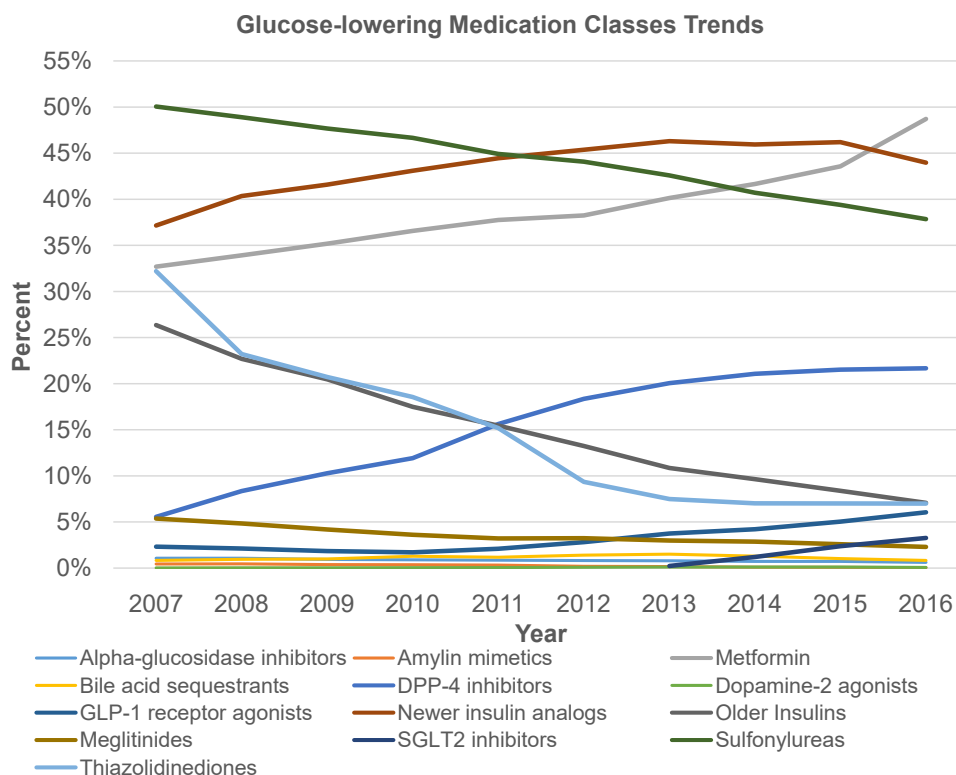
The University of Minnesota Institutional Review Board approved the study (IRB ID: STUDY00000991). Participants' informed consent was not required.

### 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, a total of 21% of patients with CKD and type 2 diabetes had no prescriptions for glucose-lowering medications. A Consolidated Standards of Reporting Trials (CONSORT) diagram for 2016 patients is provided in Fig 1. In 2016, a total of 86.3% were 65 years or older. Distributions of age and race/ethnicity were similar across yearly cohorts (Table 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 low-income subsidy status in 2016 was lower than in 2007 or 2012 (Table 1).

### Trends in Use of Glucose-Lowering Medication Classes

Several glucose-lowering medication classes showed statistically significant increases in use trends from 2007 to 2016, including metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and newer insulin analogues (Fig 2;



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

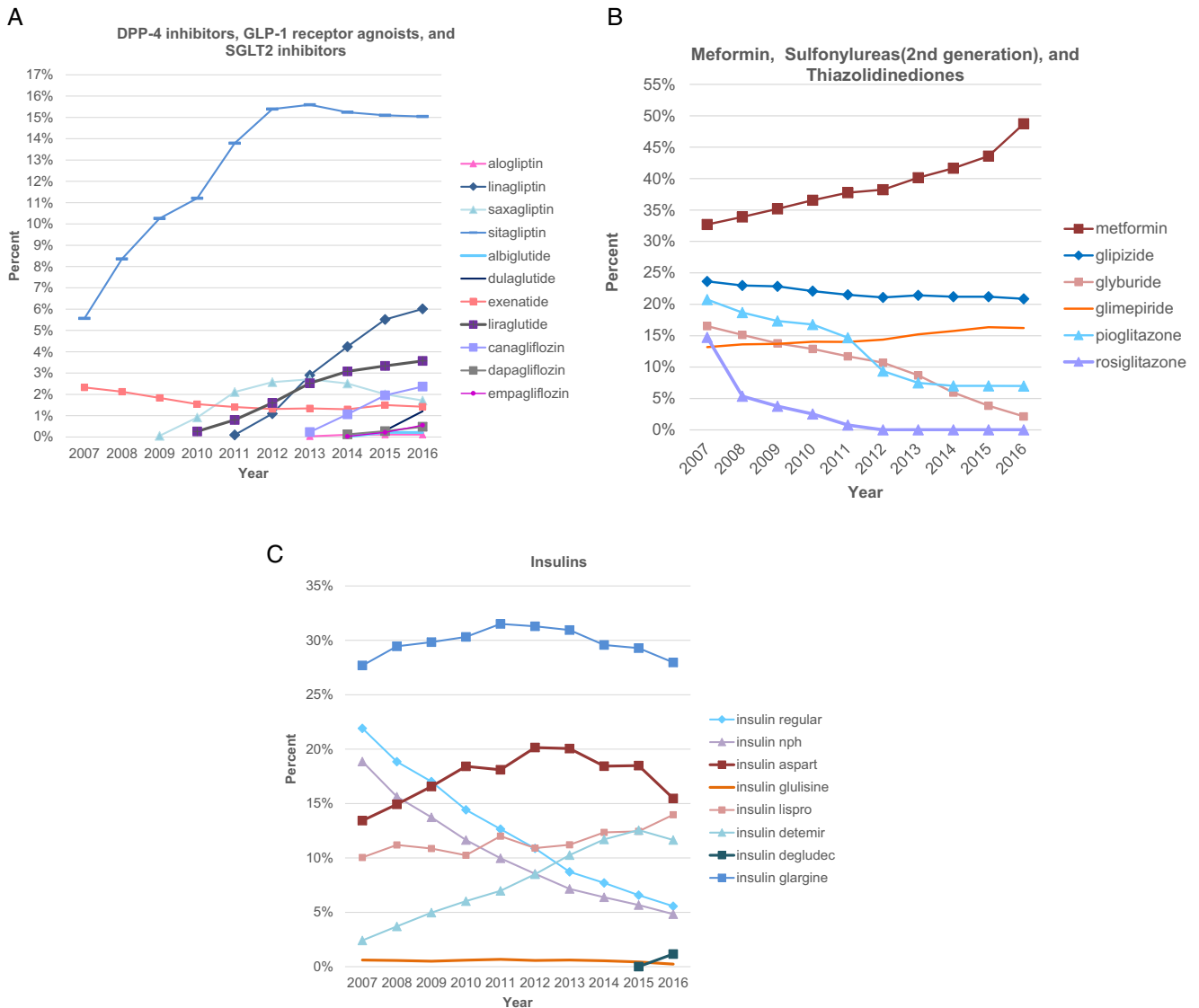
Table S5). Metformin use increased from 32.7% in 2007 to 48.7% in 2016. Use of newer classes of glucose-lowering medication increased sharply, including DPP-4 inhibitors (5.6% in 2007, 21.7% in 2016), GLP-1 receptor agonists (2.3% in 2007, 6.1% in 2016), and SGLT2 inhibitors (0.2% in 2013, 3.3% in 2016). Use of newer insulin analogues (aspart, lispro, glulisine, detemir, glargine, and 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 Fig 2.

We also examined trends in glucose-lowering medication classes by age (<65 and  $\geq$ 65 years). Patients younger than 65 years were mainly people with disabilities. Trends were similar between these age groups. However, use of sulfonylureas, newer insulin analogue insulins, or older insulins (28.6%, 59.9%, and 10.1% in 2016, respectively) among patients younger than 65 years differed from use among patients 65 years or older (39.3%, 41.5%, and 6.6% in 2016, respectively).

### 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 (Fig 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 (eg, glyburide use decreased from 16.5% to 2.2% from 2007 to 2016; Fig 3B). A large decline in the use of TZDs occurred from 2007 to 2016; rosiglitazone was essentially unused by 2012.

Use of newer analogue insulin therapy increased, especially insulin detemir (2.4% in 2007 and 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 (Fig 3C).



**Figure 3.** Trends in the use of specific glucose-lowering medications among patients with chronic kidney disease with type 2 diabetes between 2007 and 2016. Trends in: (A) dipeptidyl peptidase 4 (DPP-4) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist, and sodium-glucose cotransporter 2 (SGLT2) inhibitor use; (B) metformin, sulfonylurea (second generation), and thiazolidinedione use; and (C) insulin use. Abbreviation: nph, neutral protamine Hagedorn.

**Use of Glucose-Lowering Medication Classes by CKD Stage**

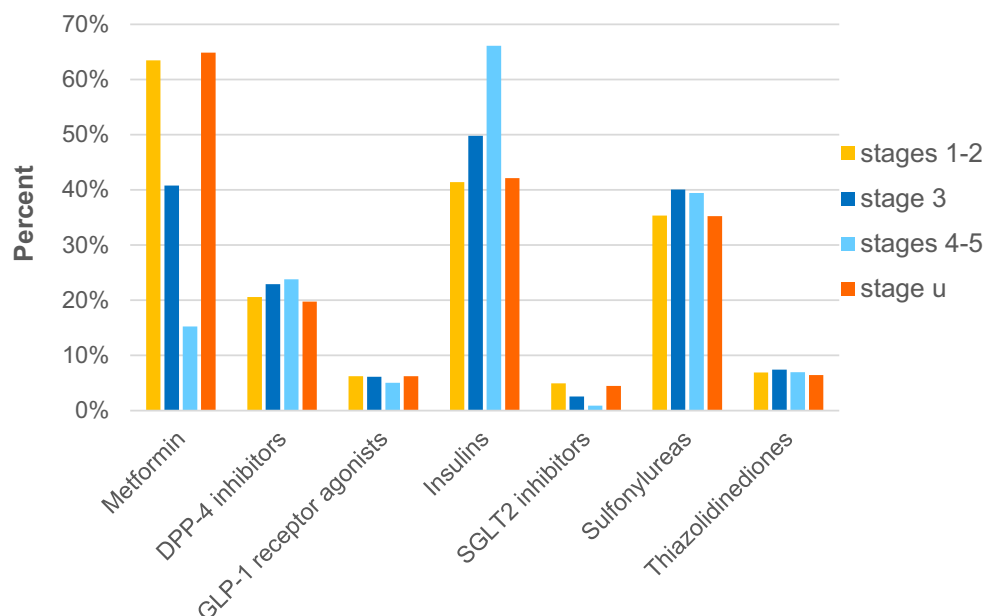
In 2016, percentages of patients with CKD with type 2 diabetes receiving insulin increased as CKD stage increased: 41% at stages 1-2 and 66% at stages 4-5. Metformin use decreased as CKD stage increased: 63% at stages 1-2 and 15% at stages 4-5. Use of DPP-4 inhibitors and GLP-1 receptor agonists was similar across CKD stages (Fig 4). Single and dual combination use of glucose-lowering medications was 49.6% and 39.9% among patients with CKD in 2016, respectively (Fig S1). The proportion of patients using 2 or more glucose-lowering medication classes decreased as CKD stage increased. Triple combination therapy was used in 16% and 9% of patients with CKD stages 1-2 and stages 4-5, respectively; quadruple

combination therapy was uncommon: 4% at stages 1-2 and 1% at stages 4-5 (Fig 5).

Among patients with CKD with diabetes who received a single glucose-lowering medication class in 2016, the most highly used class was insulin (41%; Table 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).

**DISCUSSION**

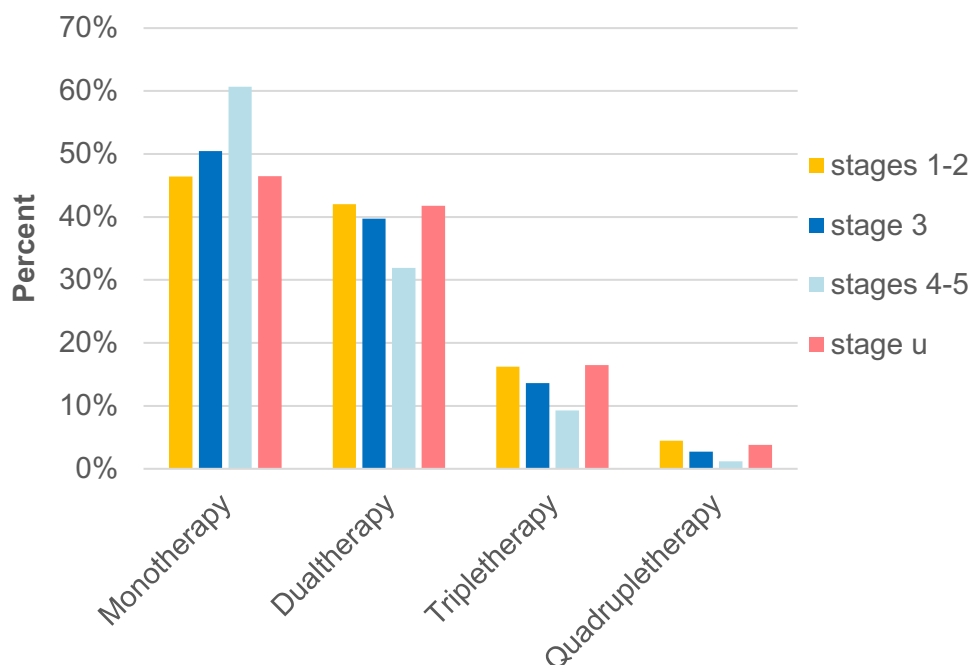
We present use patterns of glucose-lowering medications among patients with CKD based on Medicare data. Use of



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

metformin and newer glucose-lowering medication classes (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors) showed statistically significant upward trends during the study time frame. 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<sup>10</sup> published trends in and expenditures of glucose-lowering medications among US Medicare beneficiaries, 2012 to 2017. Metformin use increased during the study time frame and was the most commonly prescribed glucose-lowering medication,



**Figure 5.** Percent using monotherapy and combination therapy among patients with chronic kidney disease (CKD) with type 2 diabetes by CKD stage in 2016. Abbreviation: stage u, CKD stage unknown or unspecified.



**Table 2.** Use of Glucose-Lowering Medication Classes Among CKD Patients With Type 2 Diabetes Using Monotherapy, in 2016

Class	
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	<sup>a</sup>
Dopamine-2 agonists	<sup>a</sup>

Note: Number of patients with CKD with type 2 diabetes using monotherapy = 26,081.

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

<sup>a</sup>Counts of 10 or fewer patients.

whereas amylin analogues were the least commonly prescribed class.<sup>10</sup>

Using Medical Expenditure Panel Survey (MEPS) data from 2008 to 2015, Raval and Vyas<sup>11</sup> examined trends in glucose-lowering medication use among US individuals with diabetes and showed similar results. Use of metformin increased from 47.8% in 2008 to 59.0% in 2015, use of TZDs and sulfonylureas decreased, and use of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors increased.<sup>11</sup> We show use patterns of glucose-lowering medication classes among patients with CKD similar to those in the general population, except that insulin was the most commonly used glucose-lowering medication class in patients with CKD versus metformin in the general population. We noted a greater increase in DPP-4 inhibitor use among patients with CKD (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 2 most common dual combination therapies were metformin and sulfonylureas and metformin and insulin; the 2 most common triple combination therapies were metformin, sulfonylureas, and DPP-4 inhibitors and metformin, sulfonylureas, and insulin.<sup>11</sup> We observed the same common patterns of combination therapies in patients with CKD in 2016.

We observed an increase in metformin use in patients with CKD. In 2016, there were 63%, 41%, and 65% of patients at CKD stages 1-2, stage 3, and unspecified stage with diabetes, respectively, who used metformin. Metformin is inexpensive and effectively decreases plasma glucose levels.<sup>3</sup> The United Kingdom Prospective Diabetes Study demonstrated a reduced risk for cardiovascular events and death with metformin compared with sulfonylureas, insulin, or diet restriction among overweight patients with type 2 diabetes.<sup>12</sup> However, metformin is

mainly eliminated by the kidneys and is associated with risk for 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.<sup>13-15</sup> In 2016, the US Food and Drug Administration (FDA) requested a labeling change regarding metformin use in patients with reduced kidney function.<sup>16</sup> 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 rates (eGFRs) of 30 to 60 mL/min/1.73 m<sup>2</sup>.<sup>17</sup> Consistent with the FDA label change, ADA guidelines state that metformin is contraindicated in patients with eGFRs < 30 mL/min/1.73 m<sup>2</sup>.<sup>3,18,19</sup> Our results showed 15% metformin use in 2016 among patients with CKD stages 4-5; further investigation into the effectiveness and safety of metformin therapy in severe CKD is warranted.

We found a rapid increase in the 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 patients with CKD stages 4-5, driven by sitagliptin use. This trend was most likely due to clinician comfort with sitagliptin, given pharmacokinetic and safety studies in patients with CKD showing that a reduced dose was effective and safe even in patients receiving hemodialysis.<sup>20</sup> 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 through the bile and hence does not require dose adjustment for patients with CKD.<sup>21</sup> In contrast, all other drugs in this class (sitagliptin, saxagliptin, and alogliptin) are excreted mainly by the kidneys; ADA guidelines recommend dose adjustments in patients with CKD.<sup>3,18</sup>

The SGLT2 inhibitor class is the newest class of oral glucose-lowering medications. In March 2008, the FDA issued new guidance on the evaluation of cardiovascular risk during development of new glucose-lowering medications.<sup>22</sup> 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 for incident or worsening nephropathy (progression to macroalbuminuria, doubling of 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.<sup>5,6,23</sup> Recently, the CANVAS trial showed that canagliflozin reduced rates of the cardiovascular composite outcome, albuminuria progression, and

**Table 3.** Use of Common Glucose-Lowering Medication Classes Combination Therapy Among Patients With CKD With Type 2 Diabetes Using More Than 1 Glucose-Lowering Medication Class, in 2016

Combination Therapy	
Metformin + sulfonylurea	5,343 (20.1%)
Metformin + insulin	3,859 (14.5%)
Sulfonylurea + insulin	2,728 (10.3%)
Metformin + DPP-4 inhibitor	2,060 (7.8%)
Sulfonylurea + DPP-4 inhibitor	1,801 (6.8%)
DPP-4 inhibitor + insulin	1,710 (6.4%)
Metformin + sulfonylurea + DPP-4 inhibitor	1,432 (5.4%)
Metformin + sulfonylurea + insulin	1,368 (5.2%)
GLP-1 receptor agonist + insulin	818 (3.1%)

NOTE: Use of combination therapy  $\geq 3\%$  shown. Number of patients with CKD with type 2 diabetes using more than 1 glucose-lowering medication class = 26,545.

Abbreviations: CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.

kidney composite outcome compared with placebo among 10,142 patients with type 2 diabetes and high cardiovascular risk.<sup>24</sup> The DECLARE-TIMI 58 trial evaluated the cardiovascular safety of dapagliflozin in patients with type 2 diabetes and cardiovascular risk.<sup>25</sup> 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.<sup>26</sup> The current canagliflozin label recommends use in patients with an eGFR down to 30 mL/min/1.73 m<sup>2</sup> based on the CREDENCE trial data. The current empagliflozin and dapagliflozin labels suggest avoiding use in patients with an eGFR below 45 mL/min/1.73 m<sup>2</sup>. We anticipate that percentages of patients with CKD 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.<sup>27</sup> 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 serum creatinine level, ESKD, or death due to kidney disease.<sup>28,29</sup> 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, the efficacy of dulaglutide was similar in glycemia control, with a lower rate of hypoglycemia, smaller decline in eGFR, and greater reduction in albuminuria.<sup>30</sup> Use of these agents will likely increase in patients with CKD, 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.<sup>31</sup>

Despite FDA action that removed the prescribing and dispensing restrictions for rosiglitazone in 2013 based on new data,<sup>32</sup> rosiglitazone use remained almost nonexistent. In December 2016, the FDA announced that pioglitazone was associated with an increased risk for bladder cancer,<sup>33</sup> 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  $\sim 21\%$ . The second-generation agents (glyburide, glipizide, and glimepiride) have largely replaced first-generation drugs (chlorpropamide, tolazamide, and tolbutamide) in the general population due to lower risk for hypoglycemia. Glyburide is metabolized in the liver and excreted by the kidneys and bile,  $\sim 50\%$  by each route. Some metabolites, which have hypoglycemic activity, can accumulate in patients with CKD.<sup>34</sup> Glyburide is not recommended for patients with CKD.<sup>3</sup> An observational study by Roumie et al<sup>35</sup> compared metformin monotherapy treatment with sulfonylureas in patients with diabetes and reduced kidney function (eGFRs  $< 60$  mL/min/1.73 m<sup>2</sup>) and showed that sulfonylureas were associated with higher risk for major adverse cardiovascular events. ADA 2019 guidelines recommend metformin as the preferred first-line diabetes treatment in patients with CKD, depending on eGFR, and the best noninsulin added treatment to initial therapy is an SGLT2 inhibitor or GLP-1 receptor agonist due to their cardiovascular and kidney-related benefits.<sup>19</sup>

Use patterns of insulin in patients with CKD in our findings were similar to those in the general population.<sup>10</sup> Use of newer insulin analogues 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 increase. Meta-analysis studies demonstrated lower risk for overall and nocturnal hypoglycemia for glargine or detemir compared with NPH insulin.<sup>36,37</sup> A randomized crossover study evaluated use of the short-acting insulin analogue lispro in patients with decreased kidney function and demonstrated improvement in glycemic control and safety compared with regular insulin.<sup>38</sup> We also noted that insulin use in low-income subsidy patients was higher than in non-low-income subsidy patients (Fig S2). High out-of-pocket costs that non-low-income subsidy patients experience likely affect medication choice. The Medicare Part D program offers low-income subsidy benefits to enrollees with limited assets and income. The low-income subsidy 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 3 or higher (eGFR  $\geq$  30 mL/min/1.73 m<sup>2</sup>), metformin is the recommended first-line treatment choice because of its safety, low cost, and potential cardiovascular benefits. An SGLT2 inhibitor is recommended in the glucose-lowering treatment regimen. In patients who have not achieved individualized glycemic targets despite use of metformin and an SGLT2 inhibitor or who are unable to use those medications, a GLP-1 receptor agonist is recommended.<sup>39</sup>

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.<sup>40</sup> 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 use 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 the 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 the 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 patients with CKD enrolled in Medicare Part D; use 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 younger than 65 years, except people with disabilities, and we excluded patients with ESKD.

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

## SUPPLEMENTARY MATERIAL

Figure S1. Percent using monotherapy and combination therapy among chronic kidney disease patients with type 2 diabetes using glucose-lowering medications in 2016.

Figure S2. Trend of insulins use among chronic kidney disease patients with type 2 diabetes from 2007 to 2016, by low-income subsidy status.

Table S1. Glucose-lowering medication classes and medications

Table S2. ICD-9/10-CM diagnosis codes for chronic kidney disease

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

Table S4. ICD-9/10-CM diagnosis codes for chronic kidney disease stages

Table S5. GEE model estimation for change in overall trends of glucose-lowering medication classes from 2007 to 2016 in CKD patients with type 2 diabetes

## ARTICLE INFORMATION

**Authors' Full Names and Academic Degrees:** Julie Z. Zhao, MPH, Eric D. Weinhandl, PhD, MS, Angeline M. Carlson, PhD, and Wendy L. St. Peter, PharmD.

**Authors' Affiliations:** Department of Pharmaceutical Care & Health Systems, University of Minnesota, College of Pharmacy (JZZ, EDW, AMC, WLS); and Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN (JZZ, EDW, WLS).

**Address for Correspondence:** Julie Z. Zhao, MPH, Department of Pharmaceutical Care & Health Systems, College of Pharmacy, University of Minnesota., 7-164 Weaver-Densford Hall, 308 SE Harvard St, Minneapolis, MN 55455. E-mail: [zhaox086@umn.edu](mailto:zhaox086@umn.edu)

**Authors' Contributions:** Research idea and study design: JZZ, AMC, WLS; data acquisition: JZZ, WLS; data analysis/interpretation: JZZ, EDW, WLS; statistical analysis: JZZ, EDW, WLS; supervision or mentorship: WLS. 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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## What are the trends in utilization of glucose-lowering medications in CKD patients with Type 2 diabetes?



Cohort and Study Design	Findings		
<p> Retrospective observational cohort study</p> <p> n = 19,257 (2007) n = 52,626 (2016)</p> <p> Medicare 5% random sample</p> <p> Chronic kidney disease (CKD)</p> <p> Type 2 diabetes</p> <p> Jan 2007 - Dec 2016</p>	<p><b>Increased use of</b></p> <p> Metformin 32.7% (2007) 48.7% (2016)</p> <p> Newer classes of glucose-lowering medications DPP-4 Inhibitors, GLP-1 receptor agonists, SGLT2 Inhibitors</p> <p> Newer Insulin analogs Aspart, Lispro, Glulisine, Detemir, Glargine, Degludec 37.2% (2007) 46.3% (2013)</p>	<p><b>Decreased use of</b></p> <p> Sulfonylureas</p> <p> Thiazolidinediones</p> <p> Older Insulins Regular, NPH</p> <p> Alpha-glucosidase Inhibitors</p> <p> Amylin mimetics</p> <p> Meglitinide</p>	<p><b>Insulin</b></p> <p> Most highly used single medication class (41%)</p> <p>Use higher among low-income subsidy status patients</p> <hr/> <p><b>Combination therapy</b></p> <p> Less commonly used as CKD stage progressed</p>

**Conclusion:** Use of metformin and newer glucose-lowering medication classes is increasing in CKD patients, including in CKD stages 3 and 4, with type 2 diabetes.

**Reference:** Zhao JZ, Weinhandl ED, Carlson AM, et al. Glucose-Lowering Medication use in CKD: Analysis of US Medicare Beneficiaries between 2007 and 2016. *Kidney Medicine*, 2021. Visual Abstract by Arun Rajasekaran, MD  @nephronpower