

Glucose-Lowering Treatment Patterns in Patients With Diabetic Kidney Disease

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Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) in the United States,¹ and approximately 40% of patients with T2D have CKD.² CKD directly increases cardiovascular disease risk, the leading cause of morbidity and mortality in the T2D population.³ CKD attributed to diabetes, referred to as diabetic kidney disease (DKD), is the most common cause of end-stage renal disease.³

Poor glycemic control has been associated with DKD progression.⁴ Optimizing glucose control while slowing the progression of CKD has been a long-established goal in treating patients with DKD.³ However, many glucose-lowering drugs (GLDs) either are contraindicated or require careful dose adjustment in patients with DKD because the accumulation of active metabolites of GLDs may cause severe adverse effects (AEs) or hypoglycemia in patients with impaired renal function because of their altered metabolism and kidney clearance.^{5,6} In addition, accumulation of uremic toxins, inflammatory factors, and oxidative stress associated with CKD progression can induce insulin resistance.⁷

The impact of GLDs on renal function among patients with T2D and CKD have been designated as primary outcomes in recent clinical trials, including the CREDENCE, FLOW, and DAPA-CKD trials.⁸⁻¹¹ Renal outcomes as secondary end points have been reported in many completed clinical trials of GLDs.^{8,12-16} The results from these trials aim to provide insights on using GLDs in patients with DKD.

Furthermore, researchers have also generated real-world evidence of the impact of GLDs on renal outcomes, in addition to their impact on glycemic outcomes.¹⁷⁻²¹ Based on an electronic health record database in the United States, Boye et al found that initiating glucagon-like peptide-1 receptor agonists (GLP-1 RAs), compared with other GLDs, was associated with significantly smaller declines in estimated glomerular filtration rates (eGFRs) and larger reductions in hemoglobin A_{1c} (HbA_{1c}) over 1 year.¹⁹ The authors also reported similar findings in a later study that compared initiating dulaglutide, a GLP-1 RA agent, with insulin glargine.²⁰ Evidence from health systems outside of the United States have also demonstrated the beneficial impacts on renal outcomes from the use of sodium-glucose cotransporter-2 (SGLT) inhibitors.^{17,18,21-23}

ABSTRACT

OBJECTIVES: Recent trials of glucose-lowering drugs (GLDs) have drawn attention to renal outcomes. Our goal was to understand how patients with diabetic kidney disease (DKD) are treated in general practices in the United States.

STUDY DESIGN: Retrospective cohort study using a national-level claims data set and electronic health records.

METHODS: Patients (≥ 18 years) with type 2 diabetes, whose estimated glomerular filtration rates (eGFRs) were between 15 and 89 mL/min/1.73 m² between 2016 and 2018, were selected. Use of different GLDs during a 12-month period was examined across all eGFR levels.

RESULTS: Of the 25,486 sample patients, 69.2%, 18.9%, 9.6%, and 2.3% had an eGFR in the ranges of 60 to 89, 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73 m², respectively. Metformin was used by nearly 33% of patients with an eGFR of 30 to 44 mL/min/1.73 m² and by 10% of patients with an eGFR less than 30 mL/min/1.73 m². Less than 10% (across all eGFR levels) of patients used glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors. Use of insulin was more frequent among patients with a lower eGFR ($P < .05$). The findings were similar in subgroups with different hemoglobin A_{1c} levels (< 7% and ≥ 7%).

CONCLUSIONS: Real-world treatment of DKD in the United States is suboptimal. Inappropriate use of some GLD classes, especially in advanced DKD stages, was found along with lower than expected use of modern agents that are considered safe and effective to treat glycemic outcomes. Efforts may be needed to improve understanding of safety, glycemic efficacy, and overall clinical value of GLDs across DKD stages.

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TAKEAWAY POINTS

Our data demonstrate that real-world treatment of diabetic kidney disease (DKD) in the United States is inconsistent with the current guidelines, which may result in suboptimal outcomes.

- ▶ Use of glucose-lowering drugs (GLDs) contraindicated in advanced DKD was observed.
- ▶ Use of modern, noninsulin GLDs, which not only are effective for glucose control but have proven beneficial effects on cardiorenal outcomes, was lower than expected, even among patients with advanced DKD.
- ▶ Given the limited pharmacologic options to treat advanced DKD, efforts are needed to improve understanding of safety, glycemic efficacy, and overall clinical value of GLDs across DKD stages.

However, data on GLD treatment patterns among patients with DKD in the United States are scarce. Based on national survey data from 2007 to 2012, Wu et al reported that GLD use was consistent with treatment guidelines published in 2012 by the National Kidney Foundation.²⁴ On the other hand, using a large claims data set, Rhee et al found that GLD use in 2014 was not consistent with recent treatment guidelines regardless of CKD severity; they did not, however, examine the use of SGLT2 inhibitors.²⁵ Use of some GLD classes, including metformin, dipeptidyl peptidase-4 (DPP4) inhibitors, GLP-1 RAs, and SGLT2 inhibitors, increased noticeably from 2007 to 2016 among Medicare beneficiaries who had CKD and T2D,²⁶ and a steadily increasing trend of initiating SGLT2 inhibitors and GLP-1 RAs was observed between January 2013 and March 2020 among patients with DKD.²⁷ However, utilization of new agents remains low.²⁶

More evidence on GLD use among patients with DKD is needed to investigate how the recent developments in treatments are reflected in prescription patterns of general practitioners in the United States. Thus, the purpose of this study was to describe real-world use of GLDs in patients with T2D and renal impairment in the United States and to understand how GLD use varies by severity of renal impairment and by HbA_{1c} levels.

METHODS

Data Source

The IBM MarketScan Explorys Claims–Electronic Medical Record (EMR) data were used in this study. This data set links patients' longitudinal treatment and medical claims from the MarketScan Commercial and Medicare Supplemental databases to the same patients' clinical records from the Explorys EMR data set. The combined data set provides clinical, claims, and financial data to support health economics and outcomes research, market research, and epidemiologic analyses. All databases are compliant with the Health Insurance Portability and Accountability Act; institutional review board approval was not required for this study.

Study Design and Sample Selection

Patients with T2D were identified using all available data from January 1, 2015, through December 31, 2019. Patients were classified as having T2D if they had more claims with T2D diagnosis

codes (*International Classification of Diseases, Ninth Revision [ICD-9]* codes: 250.*0, 250.*2; *International Classification of Diseases, Tenth Revision [ICD-10]* code: E11) than claims with type 1 diabetes diagnosis codes (*ICD-9* codes: 250.*1, 250.*3; *ICD-10* code: E10). We estimated eGFR values for all dates between January 1, 2016, and December 31, 2018, from data on serum creatinine, age, race, and sex using the Chronic Kidney Disease–Epidemiology Collaboration equation.²⁸ Due to potential

multiple measures of eGFR for a patient, a randomization process aligned with a rolling cross-sectional study design was used to identify the index eGFR (**eAppendix Figure 1** [eAppendix available at ajmc.com]).²⁹ Each patient's index date is defined by the date corresponding to the index eGFR.

The study focused on patients with index eGFR values in the range of 15 to 89 mL/min/1.73 m² (ie, CKD stage 2 to 4) who were categorized into 4 index eGFR levels: 60 to 89, 45 to 59, 30 to 44, and 15 to 29 (the unit of eGFR is mL/min/1.73 m² if not stated otherwise). The 6-month period before each patient's index date serves as their baseline period; all patients were followed for 12 months from their index dates.

Patients were further required to have a T2D diagnosis code before July 1, 2015, to ensure that they developed CKD after having some experience managing T2D. Patients were also required to be 18 years or older as of January 1, 2016, and to have been continuously enrolled in their health and pharmacy plans during their baseline and follow-up periods. Patients were excluded if they had (1) evidence of dialysis or an eGFR less than 15 before the index date or (2) a diagnosis of gestational diabetes, pregnancy, or acute kidney injury in their baseline or follow-up periods.

Study Measures

Patient characteristics were assessed during the baseline period or as of the index date. Demographic characteristics included age, sex, race, health plan type, and index year. Clinical characteristics included the Charlson Comorbidity Index (CCI) score,³⁰ the Diabetes Complications Severity Index (DCSI) score,³¹ and HbA_{1c} level. The baseline HbA_{1c} value was based on the mean laboratory result during the baseline period and index date.

The percentage of patients using the following classes of GLDs (ie, the prevalence of use) was assessed during the follow-up period: metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), DPP4 inhibitors, GLP-1 RAs, SGLT2 inhibitors, alpha-glucosidase inhibitors (AGIs), meglitinides (MEGs), amylin agonists, and insulins (including basal insulin, bolus insulin, or premixed insulin). Prevalence was also assessed for the following regimens: oral GLDs only (as well as 1 class, 2 classes, or ≥3 classes of oral GLDs ever being used) and insulin without a GLP-1 RA prescription (with or without oral GLDs as a combination therapy), where combination therapy was defined by medications that overlapped for at least 60 days.

Statistical Analysis

Summary statistics (means and SDs for continuous measures, and counts and proportions for categorical measures) were computed and reported for all study measures stratified by their index eGFR levels. The Student *t* and χ^2 tests were used to compare continuous and categorical study measures, respectively, between patients in one index eGFR level and those in the next-worse index eGFR level (ie, eGFR 60-89 vs 45-59, eGFR 45-59 vs 30-44, and eGFR 30-44 vs 15-29). The Cochran-Armitage test for trend was also used to assess the homogeneity of treatment patterns across index eGFR levels. These analyses were repeated in subgroups defined by baseline HbA_{1c} (<7% and \geq 7%). All analyses were conducted using SAS version 9.4 (SAS Institute).

RESULTS

Patient Characteristics

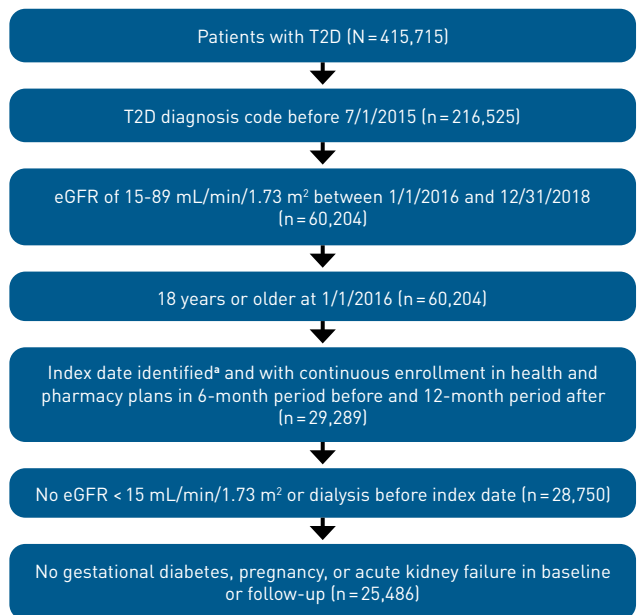
The study sample included 25,486 patients who met the sample selection criteria (Figure 1). Most patients (n=17,645; 69.2%) had index eGFR values of 60 to 89; much smaller proportions of patients had eGFR values of 45 to 59 (n=4815; 18.9%), 30 to 44 (n=2434; 9.6%), and 15 to 29 (n=592; 2.3%). Patient characteristics, summarized across index eGFR levels, are presented in the Table. Patients with eGFRs in the range of 45 to 59 were older than those in the range of 60 to 89 (mean age, 72 vs 65 years; *P* < .05). Compared with patients with eGFRs of 45 to 59, patients with eGFRs of 30 to 44 were also older and less likely to be male. No statistically significant differences in demographic characteristics were observed between patients with eGFRs of 30 to 44 and those with eGFRs of 15 to 29. Patients' mean baseline CCI and DCSI scores were higher for patients with more severe renal impairment (all *P* < .05). The mean baseline HbA_{1c} value was 7.2 to 7.3 across all eGFR levels.

Treatment Patterns

As illustrated in Figure 2, around 78% to 80% of patients across all eGFR levels were treated with GLDs. Metformin, SUs, DPP4 inhibitors, and insulin were the most used agents (>10% across all eGFR levels); less than 10% of patients used TZDs, GLP-1 RAs, SGLT2 inhibitors, or MEGs. Because so few (<1%) patients used AGIs or amylin agonists, use of these 2 agents was not reported.

Patients with higher index eGFRs were more likely to have used metformin than patients with lower eGFR values (66% among patients with eGFR values of 60 to 89 vs 10% among those with eGFR values of 15 to 29; *P* < .05). Likewise, patients with higher index eGFRs were more likely to have used GLP-1 RAs and SGLT2 inhibitors (9% and 9% among patients with eGFR values of 60 to 89 vs 6% and 1% among those with eGFR values of 15 to 29; all *P* < .05). On the other hand, patients with higher index eGFRs were less likely to have used insulin (23% among patients with eGFR values of 60 to 89 vs 45% among those with eGFR values of 15 to 29; *P* < .05). The most commonly used insulin was basal insulin, followed by bolus and premixed insulin. Also, patients with higher index eGFRs were less

FIGURE 1. Sample Selection



eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes.

*Index eGFR defined as a random value during January 1, 2016, to December 31, 2018.

likely to use SUs, DPP4 inhibitors, and MEGs (from eGFR values of 60 to 89 to eGFR values of 15 to 29, SUs: 28% to 37%; DPP4 inhibitors: 17% to 18%; MEGs: 1% to 2%; all *P* < .05).

A large proportion of patients only used oral GLDs despite an index eGFR of less than 45 (40% for eGFR values of 30 to 44 and 32% for eGFR values of 15 to 29; *P* < .05). The exclusive use of oral GLDs decreased with lower eGFR values, and a similar trend was observed when different numbers of oral GLDs (1, 2, and \geq 3 classes of oral GLDs) were examined. Further investigation showed that proportionately fewer patients with index eGFR values of 60 to 89 used insulin without a concurrent injectable GLD (ie, GLP-1 RA) than those with index eGFR values of 15 to 29 (19% vs 40%; *P* < .05). This difference was mostly driven by the use of insulin monotherapy without GLP-1 RAs or oral GLDs (7% among patients with index eGFR values of 60 to 89 vs 27% among those with index eGFR values of 15 to 29; *P* < .05).

Subgroups Defined by Baseline HbA_{1c}

The subgroups included 9392 patients with a baseline HbA_{1c} less than 7% and 8782 patients with a baseline HbA_{1c} of 7% or greater. The distributions of index eGFR levels were similar in the 2 subgroups: around 70%, 19%, 9%, and 2% had index eGFRs in the ranges of 60 to 89, 45 to 59, 30 to 44, and 15 to 29, respectively. The differences in baseline characteristics across all eGFR levels observed in the overall sample were similar in each of the HbA_{1c} subgroups (eAppendix Table).

Treatment patterns across all eGFR levels among patients with a baseline HbA_{1c} less than 7% were similar to those for the overall

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sample: Metformin, GLP-1 RAs, and SGLT2 inhibitors were less frequently used by patients with higher index eGFRs than by patients with lower index eGFRs, whereas the opposite was true for insulin, SUs, TZDs, DPP4 inhibitors, and MEGs (Figure 3). Proportionately fewer patients with higher index eGFRs exclusively used oral GLDs ($P < .05$). Use of insulin in this subgroup was noticeably less common than in the overall sample, whereas the exclusive use of oral GLDs, especially use of only 1 oral GLD class, was much more frequent.

More than 95% of patients with a baseline HbA_{1c} of 7% or greater were treated with GLDs regardless of index eGFR level (Figure 4). The proportions of patients using TZDs and DPP4 inhibitors were not statistically significantly different across all eGFR levels, whereas the relationships between use of other treatments and index eGFR values were the same as those in the overall sample. Despite having a baseline HbA_{1c} of 7% or greater, a large proportion of patients with an index eGFR less than 45 used only oral GLDs (31% and 26% of patients with index eGFR values of 30 to 44 and 15 to 29, respectively).

DISCUSSION

This study provides important evidence on how well the use of real-world GLD treatments for patients with DKD in the United States compare with the most updated guidelines published by the American Diabetes Association.³ We found that treatments for glycemic control varied by renal impairment severity. Metformin, GLP-1 RAs, and SGLT2 inhibitors were less commonly used by patients with more severe renal impairment, whereas SUs, TZDs, DPP4 inhibitors, MEGs, and insulins were more commonly used by patients with more severe renal impairment. Metformin, SUs, DPP4 inhibitors, and insulin were the most commonly used agents across all eGFR levels. These findings are consistent with evidence using earlier data.²⁵

Despite the evidence of the cardiorenal benefits of newer agents, such as GLP-1 RAs and SGLT2 inhibitors, that has been confirmed by various trials conducted since 2016,³²⁻³⁶ the utilization of these newer agents was quite low across all eGFR levels in our study—for example, less than 16% of patients with a high baseline HbA_{1c} used these agents. The suboptimal use of these newer agents may be affected by providers' established prescribing behaviors, medication costs, and/or formulary restrictions.^{37,38} Treatment decision algorithms specific to patients with DKD may be needed for health care providers, especially primary care providers³⁹; only 59% of patients in our study with eGFR values of 15 to 29 had outpatient visits to a specialist (cardiologist, endocrinologist, or nephrologist) during their follow-up periods

TABLE. Baseline Patient Characteristics by eGFR

	Index eGFR level ^a			
	60-89 (n = 17,645; 69.2%)	45-59 (n = 4815; 18.9%)	30-44 (n = 2434; 9.6%)	15-29 (n = 592; 2.3%)
Age in years, mean (SD)	65 [10.9]	72 [10.2]*	75 [9.7]*	75 [10.0]
Male, n (%)	8893 [50.4%]	2356 [48.9%]	1079 [44.3%]*	265 [44.8%]
Health plan type, n (%)		*	*	
HMO	4166 [23.6%]	1522 [31.6%]	781 [32.1%]	205 [34.6%]
PPO/POS	7931 [44.9%]	1684 [35%]	735 [30.2%]	173 [29.2%]
Comprehensive	4036 [22.9%]	1386 [28.8%]	841 [34.6%]	196 [33.1%]
Other/missing	1512 [8.6%]	223 [4.6%]	77 [3.2%]	18 [3.0%]
Index year, n (%)		*		
2016	12,925 [73.3%]	3754 [78%]	1874 [77%]	459 [77.5%]
2017	2951 [16.7%]	645 [13.4%]	337 [13.8%]	85 [14.4%]
2018	1769 [10%]	416 [8.6%]	223 [9.2%]	48 [8.1%]
CCI score, mean (SD)	3.2 [2.1]	4.0 [2.3]*	5.0 [2.7]*	5.9 [2.5]*
DCSI score, mean (SD)	3.3 [3.9]	4.5 [4.3]*	5.7 [4.8]*	8.0 [4.8]*
Baseline HbA_{1c} level, n (%)				
< 7.0%	6619 [37.5%]	1744 [36.2%]	840 [34.5%]	189 [31.9%]
7.0%-8.0%	3422 [19.4%]	938 [19.5%]	468 [19.2%]	105 [17.7%]
> 8.0%-9.0%	1472 [8.3%]	362 [7.5%]	202 [8.3%]	56 [9.5%]
> 9.0%	1245 [7.1%]	306 [6.4%]	160 [6.6%]	46 [7.8%]
Unknown	4887 [27.7%]	1465 [30.4%]	764 [31.4%]	196 [33.1%]
Baseline HbA_{1c} mean (SD) ^b	7.2 [1.4]	7.2 [1.4]	7.2 [1.4]	7.3 [1.4]

CCI, Charlson Comorbidity Index; DCSI, Diabetes Complications Severity Index; eGFR, estimated glomerular filtration rate; HbA_{1c} , hemoglobin A_{1c} ; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization.

* $P < .05$ compared with cohort with the next higher eGFR level.

^aAll eGFR levels are in mL/min/1.73 m².

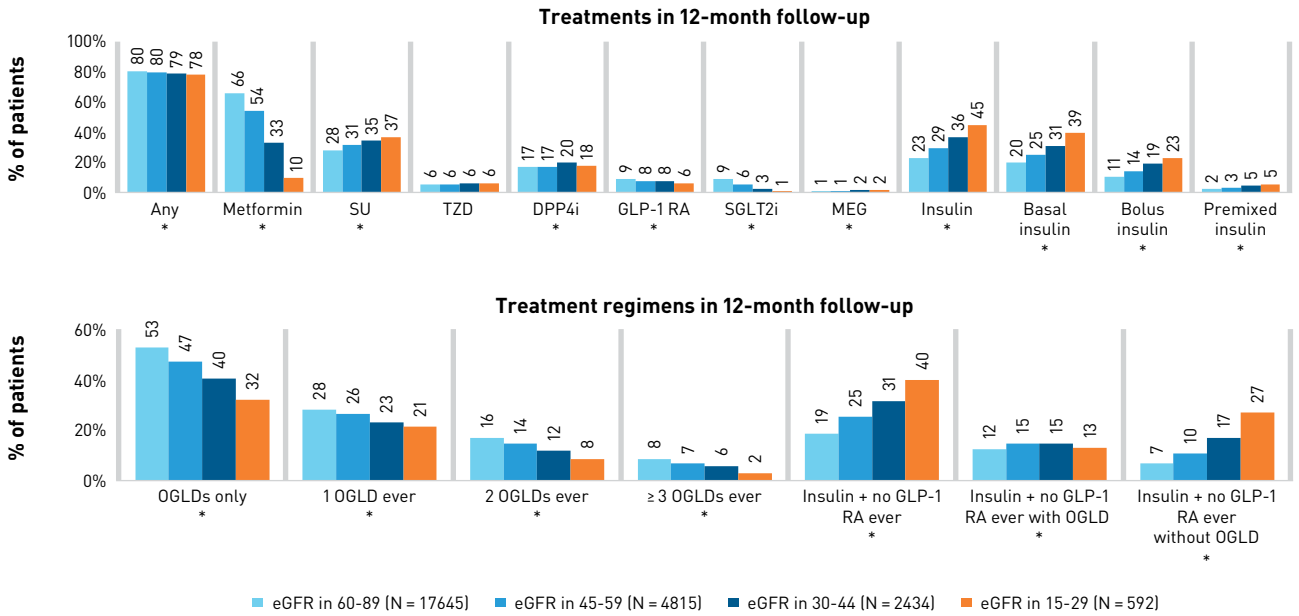
^bAmong patients with available HbA_{1c} data.

(eAppendix Figure 2). Moreover, efforts should be made to provide easier availability with better pricing of the newer agents.

A previous study, based on a 5% random sample of Medicare enrollees with CKD and T2D from 2007 to 2016, showed that the use of metformin, DPP4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors increased significantly over that time period.²⁶ A similar trend was observed in an ad hoc analysis of this study, which showed that use of GLP-1 RAs increased annually from 2016 to 2019 regardless of patients' eGFR levels (eAppendix Figure 3). This increase was noticeable for patients with low eGFR levels (from 6% in 2016 to 21% in 2019 among patients with a baseline eGFR of 15 to 29; $P < .05$). The use of SGLT2 inhibitors also increased annually, except for patients with baseline eGFR values of 15 to 29. Although the use of GLP-1 RAs and SGLT2 inhibitors increased over time, the proportion of patients using these medications remained small. Efforts are still needed to further promote using the agents that have evidence of renal and cardiovascular benefits in patients with T2D.

Although insulin has been the mainstream treatment for patients with T2D and moderate to severe CKD (eGFR values of 15-45), especially for patients with uncontrolled glycemic levels, evidence has

FIGURE 2. Treatment Pattern During 12 Months of Follow-up^a

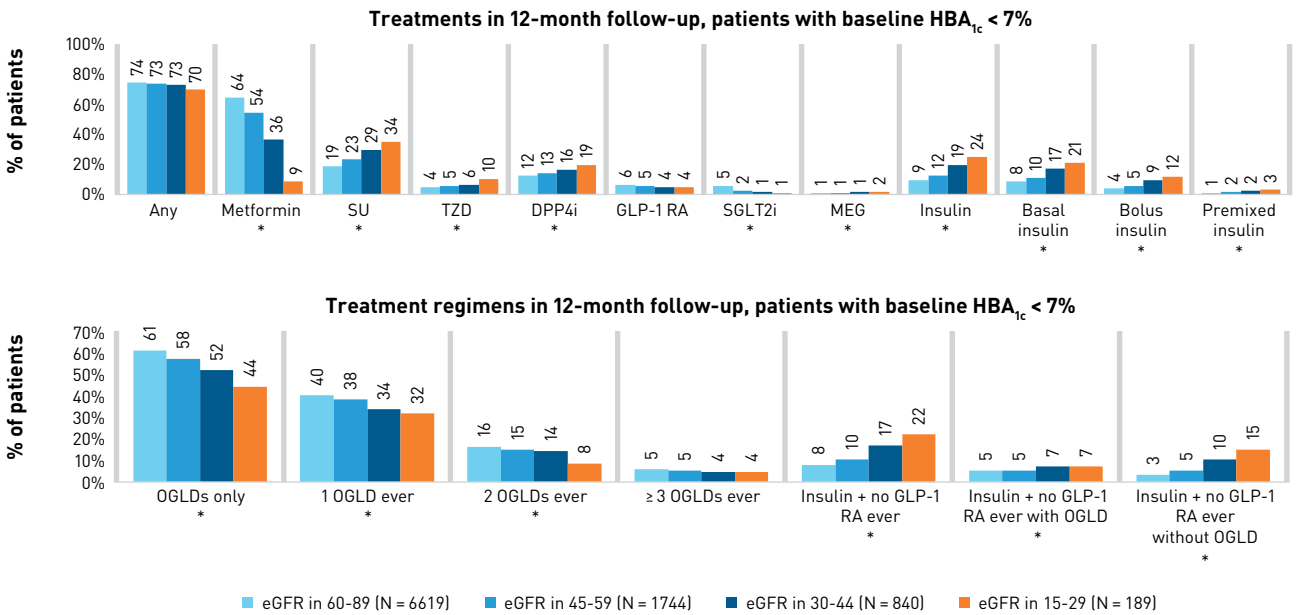


DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MEG, meglitinide; OGLD, oral glucose-lowering drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

**P* < .05 for the Cochran-Armitage test for trend.

^aAlpha-glucosidase inhibitors and amylin agonists were not presented because of < 1% use in follow-up.

FIGURE 3. Treatment Pattern Among Patients With Baseline HbA_{1c} < 7%^a

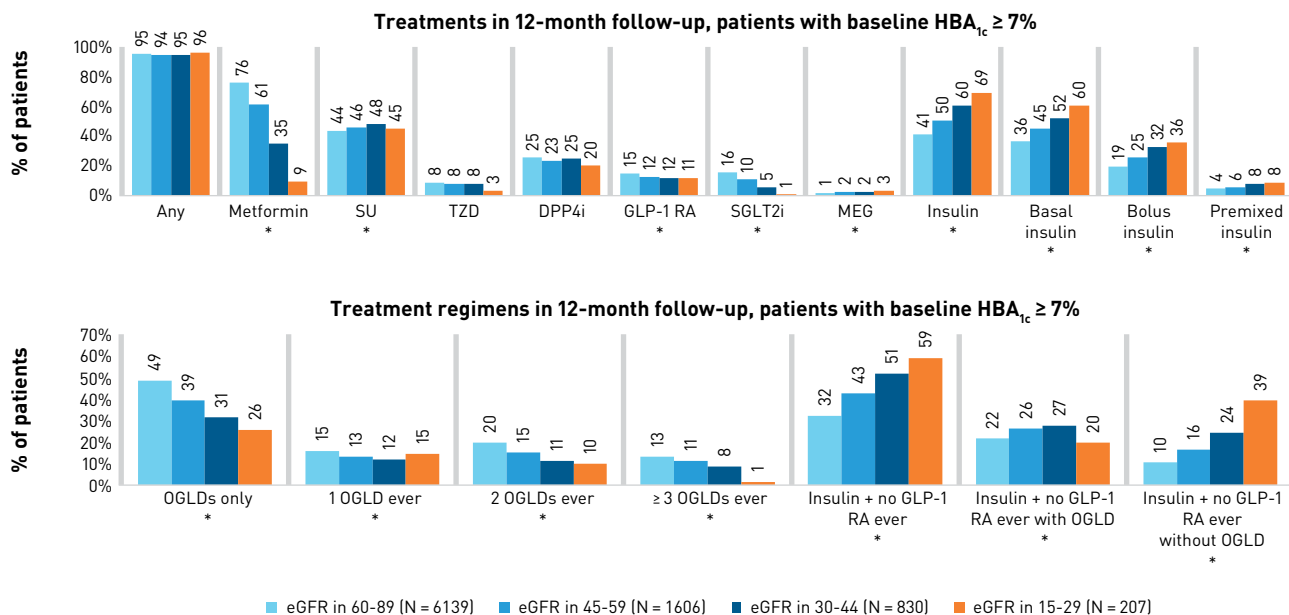


DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; MEG, meglitinide; OGLD, oral glucose-lowering drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

**P* < .05 for the Cochran-Armitage test for trend.

^aAlpha-glucosidase inhibitors and amylin agonists were not presented because of < 1% use in follow-up.

FIGURE 4. Treatment Pattern During 12 Months of Follow-up, Among Patients With Baseline HbA_{1c} ≥ 7%^a



DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; MEG, meglitinide; OGLD, oral glucose-lowering drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

*P < .05 for the Cochran-Armitage test for trend.

^aAlpha-glucosidase inhibitors and amylin agonists were not presented because of < 1% use in follow-up.

accumulated that the AEs of intensive glycemic control (hypoglycemia and mortality) have increased among patients with CKD.⁴⁰ Use of insulin was noticeably more frequent among patients with lower eGFR levels in our study. This association was most obvious for insulin monotherapy (ie, insulin without GLP-1 RAs or oral GLDs). Although insulin can be used across all eGFR levels, such therapy must be monitored and carefully titrated for patients with low eGFR levels because of increasing hypoglycemia risk. The higher risk of AEs associated with insulin use may explain the observed large proportion of patients exclusively using oral GLDs, even among patients with a baseline HbA_{1c} of 7% or greater and an eGFR less than 45.

Although metformin is the first-line treatment for T2D, it is contraindicated for patients with an eGFR less than 30 and is not recommended for patients with eGFRs between 30 and 45; increased renal function monitoring is recommended if metformin is continued in patients with an eGFR less than 45.⁴¹ Nearly one-third of patients with eGFR values of 30 to 44 used metformin in our study; more concerning is that 10% of patients with an eGFR less than 30 used this agent, which is clearly contraindicated.

SUs and DPP4 inhibitors were the most commonly used second-line noninsulin treatments in the study (> 15% of the patients used these agents across all eGFR levels). However, SUs are associated with high risk of hypoglycemia, especially among those with renal impairment, and they are also associated with weight gain; DPP4 inhibitors, however, are modestly effective at controlling blood

glucose levels without evidence of reducing cardiovascular disease or CKD progression risk.⁴² These findings, along with the high use of insulin and contraindicated use of metformin among patients with low eGFR levels, suggest that GLD treatment options for patients with advanced DKD may be limited and it is challenging to achieve glycemic control in these patients.

Limitations

Our study is subject to limitations that commonly apply to claims- and EMR-based studies, such as possible coding errors or missing data and differences in patient characteristics due to changes in data contributors. Furthermore, the database contained patients covered by commercial insurance, which may not be generalizable to the entire US population of patients with DKD. Lastly, due to the lack of albumin-to-creatinine ratio values (available in about 10% of the sample), patients' renal function status was measured only by eGFR, which may result in misclassification of CKD severity. However, these limitations should have minimal impacts on our findings as the distribution of CKD stage defined by the index eGFR in our study sample was aligned with that observed in nationally representative data.²⁴

CONCLUSIONS

Real-world treatment of DKD in the United States is suboptimal for lowering risk of cardiorenal events, as evidenced by the low usage of

noninsulin GLDs that not only effectively control blood glucose but have proven beneficial effects on renal and cardiovascular outcomes even among patients with advanced renal function decline (eGFR extending down to 15). Treatment of hyperglycemia in patients with DKD was not consistent with current guidelines, as evidenced by metformin use by patients with an eGFR less than 30. This study suggests that, given the limited pharmacologic options with which to control glucose and reduce cardiorenal risk among patients with advanced DKD, efforts may be needed to improve understanding of safety, glycemic control effectiveness, and overall clinical value of GLDs across DKD stages. ■

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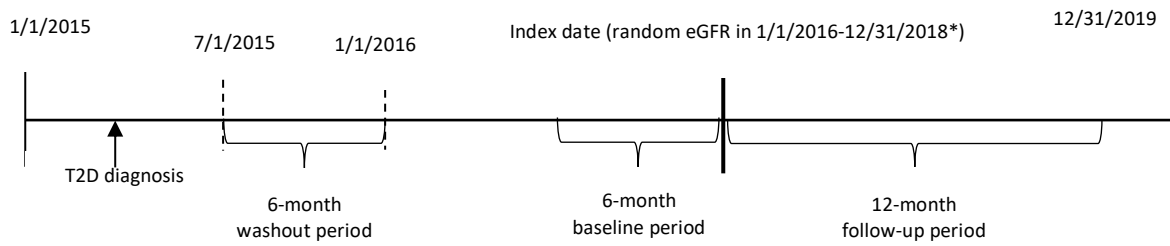
eAppendix Table. Baseline Patient Characteristics by eGFR and Baseline HbA1c

	Baseline HbA1c < 7% (N=9,392)				Baseline HbA1c ≥ 7% (N=8,782)			
	60–89 (N = 6,619; 70.5%)	45–59 (N = 1,744; 18.6%)	30–44 (N = 840; 8.9%)	15–29 (N = 189; 2.0%)	60–89 (N =6,139; 69.9%)	45–59 (N =1,606 ; 18.3%)	30–44 (N =830; 9.5%)	15–29 (N =207; 2.4%)
Age, years, mean (SD)	66 (10.7)	73 (9.5)*	76 (9.5)*	76 (9.2)	64 (10.5)	70 (10.1)*	73 (9.4)*	74 (10.1)
Male, N (%)	3,231 (48.8%)	799 (45.8%)*	342 (40.7%)	83 (43.9%)	3,312 (54%)	854 (53.2%)	398 (48%)*	92 (44.4%)*
Health plan type, N (%)		*				*	*	
HMO	1,657 (25%)	589 (33.8%)	280 (33.3%)	68 (36%)	1,594 (26%)	552 (34.4%)	275 (33.1%)	75 (36.2%)
PPO/POS	2,797 (42.3%)	537 (30.8%)	241 (28.7%)	47 (24.9%)	2,622 (42.7%)	551 (34.3%)	255 (30.7%)	60 (29.0%)
Comprehensive	1,621 (24.5%)	542 (31.1%)	292 (34.8%)	68 (36%)	1,311(21.4%)	409 (25.5%)	272 (32.8%)	63 (30.4%)
Other/missing	544 (8.2%)	76 (4.4%)	27 (3.2%)	6 (3.2%)	612 (10%)	94 (5.9%)	28 (3.4%)	9 (4.3%)
Index year, N (%)		*				*		
2016	4,948 (74.8%)	1,382 (79.2%)	665 (79.2%)	153 (81%)	4,492 (73.2%)	1,267 (78.9%)	651 (78.4%)	155 (74.9%)
2017	1,038 (15.7%)	223 (12.8%)	113 (13.5%)	27 (14.3%)	1,083 (17.6%)	225 (14%)	104 (12.5%)	28 (13.5%)
2018	633 (9.6%)	139 (8.0%)	62 (7.4%)	9 (4.8%)	564 (9.2%)	114 (7.1%)	75 (9.0%)	24 (11.6%)
CCI, mean (SD)	3 (2.1)	3.8 (2.2)*	4.8 (2.6)*	5.8 (2.4)*	3.2 (2.1)	4.1 (2.3)*	5.1 (2.6)*	6.1 (2.2)*
DCSI, mean (SD)	2.5 (3.4)	3.6 (3.9)*	4.7 (4.4)*	7.2 (4.7)*	4.3 (4.2)	5.6 (4.5)*	6.8 (5.0)*	9 (5.1)*

*p<0.05 compared to cohort with the next higher eGFR level.

CCI, Charlson Comorbidity Index; DCSI, Diabetes Complications Severity Index; HbA1c, hemoglobin; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

eAppendix Figure 1. Study Design

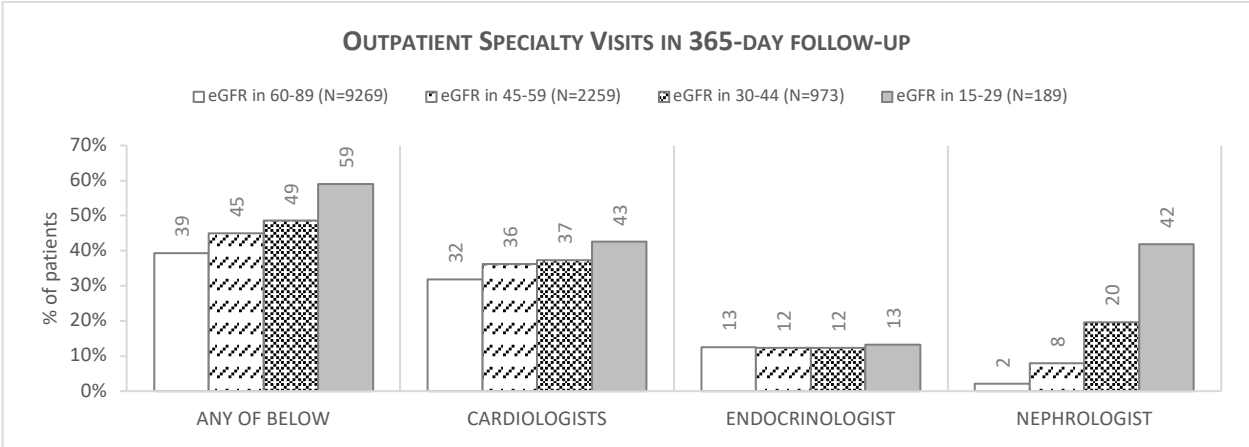


Note: The figure is not to scale.

eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes.

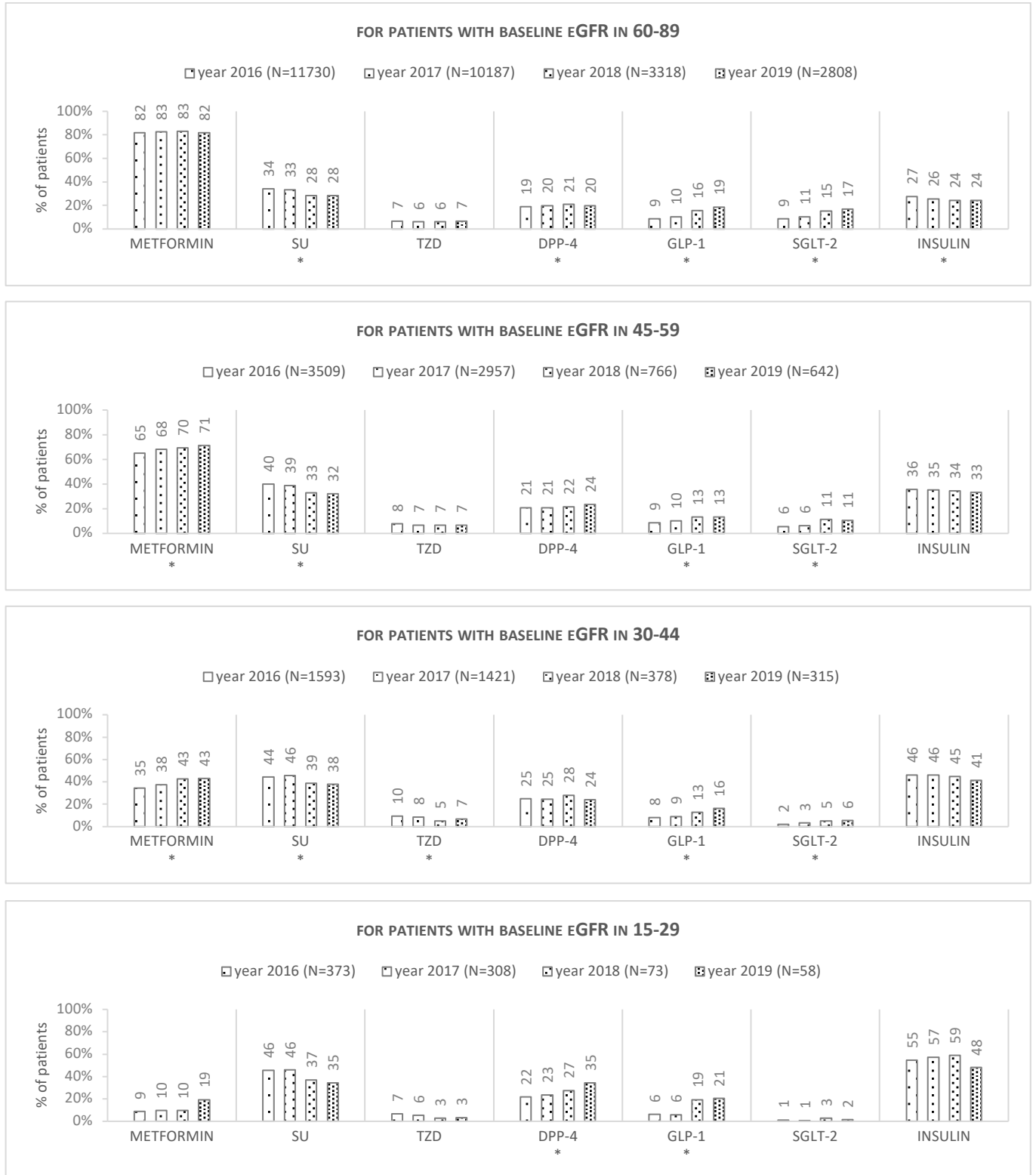
* An eGFR value was randomly selected following the uniform distribution if the patient had multiple eGFR values.

eAppendix Figure 2. Outpatient Specialty Visits in Follow-up



eGFR, estimated glomerular filtration rate

eAppendix Figure 3. Treatment Trends Over Year, Among Patients With Any GLD Use



* $p < 0.05$ for the Cochran–Armitage test for trend

Note: Baseline eGFR was defined by the average value during the six months before the calendar year.

DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.