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ORIGINAL ARTICLE

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Prescription of guideline-directed medical therapies in patients with diabetes and chronic kidney disease from the CURE-CKD Registry, 2019-2020

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Abstract

Aim: Guideline-directed medical therapy (GDMT) is designed to improve clinical outcomes. The study aim was to assess GDMT prescribing rates and prescribing-persistence predictors in patients with diabetes and chronic kidney disease (CKD) from the Center for Kidney Disease Research, Education, and Hope Registry.

Materials and Methods: Data were obtained from adults ≥18 years old with diabetes and CKD between 1 January 2019 and 31 December 2020 (N = 39 158). Baseline and persistent (≥90 days) prescriptions for GDMT, including angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide 1 (GLP-1) receptor agonist were assessed.

Results: The population age (mean ± SD) was 70 ± 14 years, and 49.6% (n = 19 415) were women. Baseline estimated glomerular filtration rate (2021 CKD-Epidemiology Collaboration creatinine equation) was 57.5 ± 23.0 ml/min/1.73 m^2 and urine albumin/creatinine 57.5 mg/g (31.7-158.2; median, interquartile range). Baseline and ≥90-day persistent prescribing rates, respectively, were 70.7% and 40.4% for ACE inhibitor/ARB, 6.0% and 5.0% for SGLT2 inhibitors, and 6.8% and 6.3% for GLP-1 receptor agonist (all $p < .001$). Patients lacking primary commercial health insurance coverage were less likely to be prescribed an ACE inhibitor/ARB [odds ratio (OR) = 0.89; 95% confidence interval (CI) 0.84-0.95; $p < .001$], SGLT2 inhibitor (OR 0.72; 95% CI 0.64-0.81; $p < .001$) or GLP-1 receptor agonist (OR 0.89; 95% CI 0.80-0.98; $p = .02$). GDMT prescribing rates were lower at Providence than UCLA Health.

Conclusions: Prescribing for GDMT was suboptimal and waned quickly in patients with diabetes and CKD. Type of primary health insurance coverage and health system were associated with GDMT prescribing.

KEYWORDS
diabetic nephropathy, elecronic health records data, kidney and cardiovascular protective drugs, real-world evidence, type 2 diabetes

1 | INTRODUCTION

The growing prevalence of chronic kidney disease (CKD), currently 37 million people in the United States and 850 million worldwide,[1] is largely attributable to a striking increase in diabetes prevalence across the globe.[2] The majority of patients with diabetes and CKD at early stages, who may have much to gain from persistent use of guideline-directed medical therapy (GDMT), are often managed in primary care and diabetes practices.[3] The angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide (GLP)-1 receptor agonist classes are currently recommended by the Kidney Disease Improving Global Outcomes Initiative, and the American Diabetes Association to reduce kidney and cardiovascular risks and improve clinical outcomes in diabetes.[4] Importantly, co-management of early stage CKD between primary care clinicians and specialists is associated with higher rates of ACE inhibitor/ARB prescribing and kidney disease monitoring.[5,6] This strategy is particularly relevant for high-risk groups, particularly disadvantaged populations who have disproportionately high rates of diabetes and CKD.[7–9]

Even though an ACE inhibitor/ARB has been the standard of care to treat diabetes and CKD for >20 years,[10–12] the US lags in prescribing these agents compared with other high-income countries.[3,13–17] Between 2006 and 2017, less than one-quarter of patients with diabetes and CKD in the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry, an electronic health records (EHR) database from Providence and the University of California, Los Angeles (UCLA) Health systems, were prescribed an ACE inhibitor/ARB.[18,19] And, despite overwhelmingly positive results from recent landmark cardiovascular and kidney disease outcomes trials for SGLT2 inhibitors and GLP-1 receptor agonists,[9–14] these classes of GDMT have been markedly underprescribed.[3,14,20–24] Greater understanding of how GDMT is used in clinical practice is needed to inform strategies to increase equitable uptake and ongoing treatment. The study aim was to assess GDMT prescribing rates and predictors of persistent prescriptions of ACE inhibitor/ARB, SGLT2 inhibitor, and GLP-1 receptor agonist classes based on demographics, clinical features, health system and care utilization, and health insurance status in a contemporary cohort of patients with diabetes and CKD.

2 | MATERIALS AND METHODS

2.1 | Data source

Data obtained from EHRs from two non-profit health systems, Providence and UCLA Health, were used to create the registry from demographics, encounters, administrative codes, laboratory measures and prescription information. Data from Providence were obtained from sites in five western states (Washington, Montana, Oregon, Alaska and California), and data from UCLA Health were obtained from affiliated hospitals and outpatient primary care clinics in the Los Angeles region. The study was approved by Providence and the UCLA Health Institutional Review Boards, who determined written informed consent was not required for analyses of a limited EHR dataset. A data use agreement between Providence and UCLA Health laid the foundation for data sharing, stewardship and security. The study was conducted according to the Reporting of Observational Studies in Epidemiology guidelines.[25]

2.2 | Study population

Adults (age ≥18 years) identified with diabetes and CKD in 2015-2020 were followed for ≥90 days between 1 January 2019 and 31 December 2020 (N = 39 158) (Figure 1). Diabetes was identified by laboratory measures (one haemoglobin A1c ≥6.5%, or two random or fasting blood glucose measures ≥200 mg/dl or ≥126 mg/dl, respectively between 1 day and 2 years apart), prescriptions for glucose-lowering agents (excluding patients with polycystic ovarian syndrome prescribed metformin and no other indications of diabetes mellitus), or administrative codes (one inpatient or two outpatient codes for diabetes).[18,26] Hypertension was captured based on at least two measurements of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, at least 14 days apart, or at least one inpatient or outpatient encounter with an ICD-9 or ICD-10 code for hypertension. CKD was identified by a combination of two laboratory measures ≥90 days apart: estimated glomerular filtration rate (eGFR; 2021 Chronic Kidney Disease-Epidemiology [CKD-EPI] equation with creatinine)[27] <60 ml/min/1.73 m^2, or urine albumin/creatinine ratio

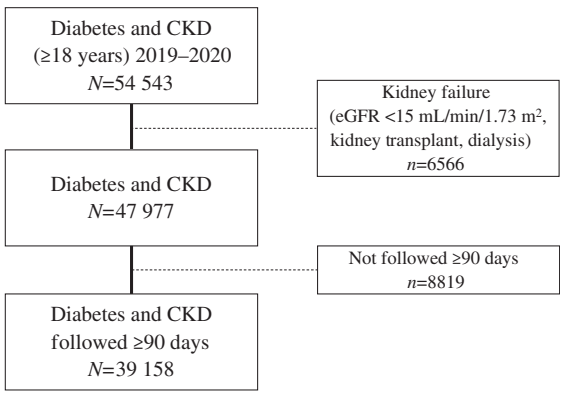


FIGURE 1 Flow diagram for study population with diabetes and CKD (N = 39 158). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

(UACR) ≥30 mg/g, or urine protein/creatinine ratio (UPCR) ≥0.15 g/g, or an administrative code indicating CKD with laboratory based confirmation by eGFR <60 ml/min/1.73 m^2, UACR ≥30 mg/g, or UPCR ≥0.15 g/g.[25] Patients with kidney failure treated by kidney transplant or dialysis or with eGFR <15 ml/min/1.73 m^2 were excluded.

2.3 | Measurements and outcomes

Demographics, type of primary health insurance coverage and prescription medication records were collected from clinical visits, and duration of follow-up time was determined from the first to the last visit during 2019-2020. Baseline measurements for eGFR, systolic blood pressure, haemoglobin A1c, UACR and UPCR were taken as the mean of values collected up to 1 year after the first clinical visit.

The primary outcome was rates of persistent prescribing that lasted ≥90 cumulative days for an ACE inhibitor/ARB as ascertained from prescription records in the EHR for an ACE inhibitor/ARB during 2019-2020. A persistently prescribed SGLT2 inhibitor (patients with eGFR ≥30 ml/min/1.73 m^2) or a GLP-1 receptor agonist were also based on prescriptions written during 2019-2020, and were secondary outcomes according to emerging clinical evidence supporting their use during the study timeframe of 2019-2020.[4]

2.4 | Statistical analyses

Categorical variables were reported as frequencies and percentages. Continuous, normally distributed variables were reported as mean ± standard deviation (SD) and continuous, non-normally distributed variables were reported as median and interquartile range (IQR). To make comparisons between variables, Pearson's chi-squared (categorical), independent samples *t*-test (normal, continuous), or Mann-Whitney U (non-normal, continuous) analyses were performed.

Multivariable, binary, logistic regression was used to identify predictors of ≥90 days persistence of medication prescribing by class (ACE inhibitors/ARBs combined into one variable, SGLT2 inhibitors, or GLP-1 receptor agonists). A model selection was performed for a set of pre-defined variables that were additively entered in to blocks by category: demographics, clinical measurements, health system and care utilization, and type of health insurance. Model performance was evaluated after each successive block addition by the Akaike information criterion and area under the receiver operating curve. Variance inflation factors were used to assess model variables for multicollinearity. Block 1 included demographic variables (age, sex, race and ethnicity) and type of health insurance. Block 2 included the variable of follow-up time (quarters). Block 3 added health system-related variables (site, hospitalization, number of outpatient clinical visits per 90 days). Block 4 added clinical variables (eGFR and hypertension status). The final block included ≥90 days of persistent prescribing of ACE inhibitor/ARB, SGLT2 inhibitor and GLP-1 receptor agonist classes, when not modelled as the outcome, and additional medication variables, including mineralocorticoid receptor antagonists (MRAs),[28,29] non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs). Use of GDMT was consistently higher for commercial insurance versus other types; therefore, insurance status was dichotomized as commercial versus non-commercial.

Sensitivity analyses evaluating model stability with eGFR calculated by the 2009 CKD-EPI equation and two extended thresholds (180- and 365-cumulative days) for ≥90 days of persistent medication prescribing were completed. Because of missing data for UACR/UPCR (51%), a sensitivity analysis was performed with macroalbuminuria (UACR >300 mg/g)/overt proteinuria (UPCR >0.5 g/g) status added to the final models for patients with these data available. Statistical significance was set a priori at $p < .05$. Univariate and bivariate analyses were completed using SAS 9.4. Multivariable modelling analyses were completed using R version 4.2.1.[30]

3 | RESULTS

3.1 | Baseline characteristics

For patients with diabetes and CKD in 2019-2020, the mean age was 70 ± 14 years and 49.6% were women (Table 1). Patients were most commonly identified as White race, but racial and ethnic composition differed by health system with fewer White patients at UCLA Health versus Providence, 48.8% and 68.3%, respectively. Over half, 56.6% of all patients were covered by Medicare as their primary form of health insurance. On the other hand, 38.8% of UCLA patients and 19.8% of Providence patients had commercial insurance as the primary coverage. Baseline mean (SD) eGFR was 57.5 ± 23.0 ml/min/1.73 m^2 and the median (IQR) UACR was 57.5 (31.7-158.2) mg/g.

At baseline, an ACE inhibitor/ARB was prescribed to 70.7% of patients with diabetes and CKD in proportions that were similar for the two health systems. SGLT2 inhibitors were prescribed to 6.0% and GLP-1 receptor agonists were prescribed to 6.8%, at rates that were higher at UCLA Health versus Providence ($p < .001$) (Table 2). In contrast, baseline prescribing of conventional MRAs and NSAIDs was 9.8% and 37.7%, respectively, which was significantly higher at Providence versus UCLA Health ($p < .001$). Baseline prescribing of PPIs was 40.8% with similar proportions at each health system (Table 2).

3.2 | Persistence patterns of prescribing guideline-directed medical therapy

The median (IQR) follow-up time was 6.5 (3.8-7.7) quarters, or about 1.5 years, with longer time at UCLA Health versus Providence, 7.2 (4.7-7.9) versus 6.3 (3.7-7.6) quarters during 2019-2020. Overall, 40.4% of patients with diabetes and CKD had an ACE inhibitor/ARB prescription that lasted ≥90 days with a significant difference

TABLE 1 Baseline characteristics of patients with diabetes and CKD in 2019-2020

	Total	UCLA health	Providence	
	N = 39 158	n = 8165	n = 30 993	*p*-Value
Demographics				
Sex, n (%)				<.001
Men	19 743 (50.4)	4341 (53.2)	15 402 (49.7)	
Women	19 415 (49.6)	3824 (46.8)	15 591 (50.3)	
Age, years; mean (SD)	70 (14)	69 (14)	70 (13)	<.001
Race and ethnicity, n (%)				<.001
American Indian or Alaska Native	352 (0.9)	42 (0.5)	310 (1.0)	
Asian	3210 (8.2)	1030 (12.6)	2180 (7.0)	
Black	2266 (5.8)	668 (8.2)	1598 (5.2)	
Hispanic or Latino(a)	1596 (4.1)	472 (5.8)	1124 (3.6)	
Native Hawaiian or Pacific Islander	484 (1.2)	22 (0.3)	462 (1.5)	
White	25 142 (64.2)	3981 (48.8)	21 161 (68.3)	
Other[a]	4546 (11.6)	1342 (16.4)	3204 (10.3)	
Not reported	1562 (4.0)	608 (7.4)	954 (3.1)	
Primary health insurance, *n* (%)				<.001
Medicare	22 169 (56.6)	4756 (58.2)	17 413 (56.2)	
Medicaid	2455 (6.3)	231 (2.8)	2224 (7.2)	
Commercial	9313 (23.8)	3172 (38.8)	6141 (19.8)	
Uninsured	4041 (10.3)	-	4041 (13.0)	
Unknown	1180 (3.0)	6 (0.1)	1174 (3.8)	
Clinical features				
Follow-up time, quarters, median (IQR)	6.5 (3.8-7.7)	7.2 (4.7-7.9)	6.3 (3.7-7.6)	<.001
Hypertension, n (%)	34 000 (86.8)	7165 (87.8)	26 835 (86.6)	.01
eGFR 2021, ml/min/1.73 m^2				
n (%)	39 158 (100.0)	8165 (100.0)	30 993 (100.0)	
Mean (SD)	57.5 (23.0)	62.5 (24.5)	56.2 (22.4)	<.001
KDIGO CKD stage by eGFR, ml/min/1.73 m^2				<.001
1 (≥90), n (%)	4970 (12.7)	1485 (18.2)	3485 (11.2)	
2 (60-89), n (%)	5641 (14.4)	1507 (18.5)	4134 (13.3)	
3a (45-59), n (%)	17 372 (44.4)	3298 (40.4)	14 074 (45.4)	
3b (30-44), n (%)	8144 (20.8)	1405 (17.2)	6739 (21.7)	
4 (15-29), n (%)	3031 (7.7)	470 (5.8)	2561 (8.3)	
Systolic blood pressure, mmHg				
n (%)	36 994 (94.5)	8039 (98.5)	28 955 (93.4)	
Mean (SD)	133 (17)	133 (16)	134 (17)	.19
HbA1c, %				
n (%)	25 798 (65.9)	6454 (79.0)	19 344 (62.4)	
Median (IQR)	6.9 (6.3-8.0)	6.7 (6.2-7.7)	7.0 (6.3-8.1)	<.001
UACR				
n (%)	17 783 (45.4)	5047 (61.8)	12 736 (41.1)	
Median (IQR)	57.5 (31.7-158.2)	54.7 (33.0-141.0)	59.1 (31.0-164.2)	.80
<30 mg/g, n (%) with UACR measures	3934 (22.1)	972 (19.3)	2962 (23.3)	<.001
30-300 mg/g, n (%) with UACR measures	11 041 (62.1)	3311 (65.6)	7730 (60.7)	
>300 mg/g, n (%) with UACR measures	2808 (15.8)	764 (15.1)	2044 (16.0)	

TABLE 1 (Continued)

	Total	UCLA health	Providence	
	N = 39 158	n = 8165	n = 30 993	*p*-Value
UPCR				
n (%)	2025 (5.2)	100 (1.2)	1925 (6.2)	
Median (IQR)	0.5 (0.2-1.7)	0.3 (0.2-1.4)	0.5 (0.2-1.7)	.07
<0.15 g/g, n (%) with UPCR measures	338 (16.7)	20 (20.0)	318 (16.5)	.31
0.15-0.5 g/g, n (%) with UPCR measures	729 (36.0)	40 (40.0)	689 (35.8)	
>0.5 g/g, n (%) with UPCR measures	958 (47.3)	40 (40.0)	918 (47.7)	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; IQR, interquartile range; N, overall sample size; n, by group sample size; SD, standard deviation; UACR, urine albumin/creatinine ratio; UCLA, University of California Los Angeles Health; UPCR, urine protein/creatinine ratio.
[a]Includes participants that did not identify with main US Census Bureau categories.

TABLE 2 Medication prescribing rates in patients with diabetes and CKD in 2019-2020

	Total	UCLA	Providence	
	N = 39 158	n = 8165	n = 30 993	*p*-Value
Medications at baseline, n (%)				
ACE inhibitor/ARB	27 690 (70.7)	5839 (71.5)	21 851 (70.5)	.07
SGLT2 inhibitor[a]	2156 (6.0)	847 (11.0)	1309 (4.6)	<.001
GLP-1 receptor agonist	2663 (6.8)	848 (10.4)	1815 (5.9)	<.001
MRA	3870 (9.8)	721 (8.8)	3149 (10.2)	<.001
NSAID	14 773 (37.7)	2723 (33.3)	12 050 (38.9)	<.001
PPI	15 991 (40.8)	3407 (41.7)	12 584 (40.6)	.07
GDMT prescribing persistence ≥90 days, n (%)				
ACE inhibitor/ARB[b]	15 806 (40.4)	4248 (52.0)	11 558 (37.3)	<.001
SGLT2 inhibitor[a,b]	1809 (5.0)	780 (10.1)	1029 (3.6)	<.001
GLP-1 receptor agonist[b]	2477 (6.3)	897 (11.0)	1580 (5.1)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; GLP, glucagon-like peptide; MRA, mineralocorticoid receptor antagonist; N, overall sample size; n, by group sample size; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SGLT, sodium-glucose cotransporter; UCLA, University of California Los Angeles Health.
[a]SGLT2 inhibitor use in cohort excluding patients with mean baseline eGFR <30 ml/min/1.73 m^2 based on KDIGO Diabetes and Chronic Kidney Disease guideline in 2020.[4]
[b]$p < .001$ for baseline versus ≥90 days persistence of GDMT prescriptions for each comparison (Total, UCLA and Providence).

between UCLA Health and Providence, 52.0% versus 37.3% (Table 2). Of those prescribed an ACE inhibitor/ARB at baseline, 51.4% persisted ≥90 days with the median (IQR) time for persistence of 401 (237-588) days. Prescribing of an SGLT2 inhibitor for ≥90 days was observed in 5.0% of patients with significantly higher persistent prescribing rates also at UCLA Health compared with Providence. In those prescribed SGLT2 inhibitors at baseline, 46.4% persisted ≥90 days with median (IQR) time for persistence of 376 (217-574) days. GLP-1 receptor agonist prescriptions persisted for ≥90 days in 6.3% of patients, with significantly higher rates at UCLA Health compared with Providence. In those prescribed a GLP-1 receptor agonist at baseline, 51.8% persisted ≥90 days with median (IQR) time for persistent prescribing of 398 (238-597) days.

3.3 | Prescribing patterns of guideline-directed medical therapy by health insurance status

GDMT prescribing patterns differed significantly by health insurance coverage (Table 3). Specifically, ≥90 days persistence of an ACE inhibitor/ARB was highest for patients with a primary commercial insurance (45.9%) compared with the uninsured (44.2%), or those with either Medicare (37.7%), or Medicaid (35.4%) as the primary insurance coverage ($p < .001$). Similarly, ≥90 days persistence of SGLT2 inhibitors was highest for patients with primary commercial insurance (9.4%) compared with the uninsured (4.7%), or those with Medicare (3.3%), or Medicaid (4.2%) primary insurance coverage ($p < .001$). Persistence of GLP-1 receptor agonists ≥90 days was also highest for

TABLE 3 Primary health insurance coverage in patients with diabetes and chronic kidney disease who had ≥90 days persistent guideline-directed medical therapy in 2019-2020

	Medicare	Medicaid	Uninsured	Unknown	Commercial	
	N = 22 169	N = 2455	N = 4041	N = 1180	N = 9313	*p*-Value
n (%)						
ACE inhibitor/ARB	8361 (37.7)	868 (35.4)	1787 (44.2)	513 (43.5)	4277 (45.9)	<.001
GLP-1 receptor agonist	971 (4.4)	146 (5.9)	278 (6.9)	84 (7.1)	998 (10.7)	<.001
	Medicare	Medicaid	Uninsured	Unknown	Commercial	
	N = 20 215	N = 2194	N = 3809	N = 1131	N = 8778	*p*-value
n (%)						
SGLT2 inhibitor[a]	667 (3.3)	93 (4.2)	178 (4.7)	45 (4.0)	826 (9.4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GLP, glucagon-like peptide; SGLT2, sodium-glucose cotransporter 2.

[a]Excluding patients with eGFR <30 ml/min/1.73 m^2.

those with primary commercial insurance (10.7%) compared with uninsured (6.9%), and Medicare (4.4%) or Medicaid (5.9%) primary insurance coverage ($p < .001$).

3.4 | Predictors of guideline-directed medical therapy prescribing patterns

The odds of ≥90 days persistent prescribing patterns of GDMT were lower for patients with diabetes and CKD who did not have primary commercial insurance [ACE inhibitor/ARB: odds ratio (OR) 0.89, 95% confidence interval (CI) 0.84-0.95, $p < .001$; SGLT2 inhibitor: OR 0.72, 95% CI 0.64-0.81, $p < .001$; GLP-1 receptor agonist: OR 0.89, 95% CI 0.80-0.98, $p = .02$) and for those treated at Providence compared with UCLA Health (ACE inhibitor/ARB: OR 0.74, 95% CI 0.70-0.78, $p < .001$; SGLT2 inhibitor: OR 0.54, 95% CI 0.49-0.61, $p < .001$; GLP-1 receptor agonist: OR 0.74, 95% CI 0.67-0.81, $p < .001$). In patients who had hospitalizations, the odds of ≥90 days persistent GDMT prescribing were also lower for SGLT2 inhibitors (OR 0.66, 95% CI 0.57-0.77, $p < .001$) and GLP-1 receptor agonists (OR 0.61, 95% CI 0.54-0.69, $p < .001$), but not for an ACE inhibitor/ARB. Conversely, persistent GDMT prescribing for ≥90 cumulative days increased significantly as follow-up time increased and with higher eGFR (Figure 2A-C, Table S1).

ACE inhibitor/ARB prescribing persistence for ≥90 days was higher in men and those with hypertension, non-White race, older age and in those who were prescribed an SGLT2 inhibitor, GLP-1 receptor agonist, MRA, PPI or NSAID (Figure 2A-C, Table S1). SGLT2 inhibitor prescribing persistence ≥90 days was also higher for men, non-White race and with use of an ACE inhibitor/ARB, GLP-1 receptor agonist, or MRA (Figure 2B, Table S1). The odds of ≥90 days persistent SGLT2 inhibitor prescribing were lower for those with hypertension and older age. GLP-1 receptor agonist prescribing persistence ≥90 days was higher with prescribing of an SGLT2 inhibitor or an ACE inhibitor/ARB (Figure 2C, Table S1) and lower for older patients. ACE inhibitor/ARB persistence was 38% (9605/25142) in White and 44% (6201/14016) in non-White groups. For SGLT2 inhibitors, the persistence rate was 4% (949/23225) and 7% (860/12902) in White and non-White groups, respectively. For GLP-1 receptor agonists, the persistence rate was 6% (1400/25142) and 8% (1077/14016) in White and non-White groups, respectively. Although differences in GDMT persistence existed between White and non-White groups, no interactions between race and insurance status were observed.

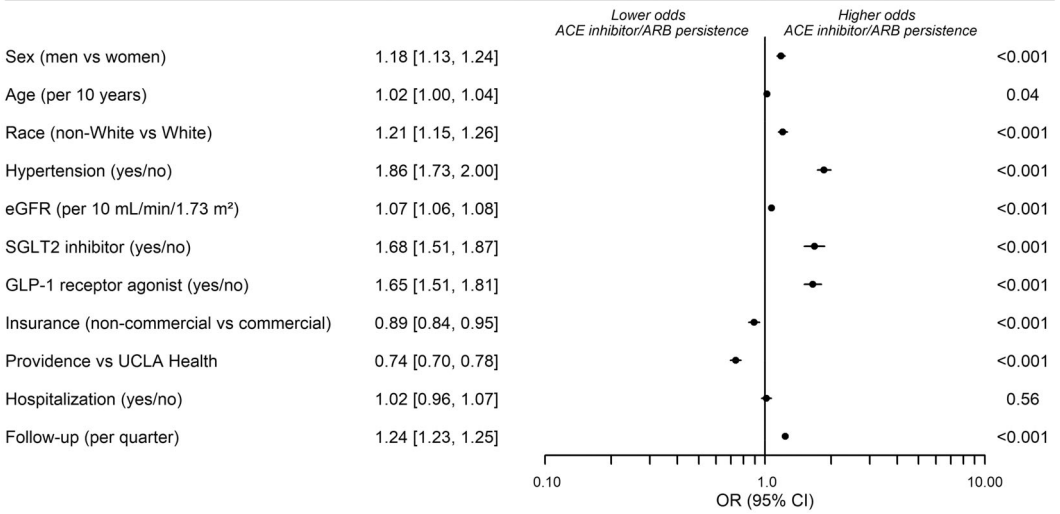
3.5 | Sensitivity analysis

In a sensitivity analysis, the 2009 CKD-EPI eGFR equation produced a comparable model with the 2021 CKD-EPI equation. Models for sensitivity analyses with 180 and 365 days of GDMT prescribing persistence ≥90 days were consistent with the main analysis. For patients with available measures, macroalbuminuria (UACR >300 mg/g)/overt proteinuria (UPCR >0.5 g/g) was a significant predictor of ≥90 days persistent prescribing of an ACE inhibitor/ARB (OR 1.29, 95% CI 1.19-1.40, $p < .001$) or a GLP-1 receptor agonist (OR 1.18, 95% CI 1.04-1.34, $p = .01$) and did not confound other model variables (Table S2).

4 | DISCUSSION

GDMT was substantially under-prescribed in patients with diabetes and CKD in two major US health systems during 2019-2020. Moreover, GDMT prescribing rates dropped quickly following baseline. While an ACE inhibitor/ARB was initially prescribed to 70.7%, a considerable improvement over earlier periods,[18] the rate dropped to 40.4% after 90 days. Notably, patients without commercial health insurance as their primary coverage were less likely to be prescribed an SGLT2 inhibitor or GLP-1 receptor agonist at baseline, or persistently prescribed an ACE inhibitor/ARB, SGLT2 inhibitor, or GLP-1 receptor agonist for ≥90 days. Prescribing rates and persistence of GDMT prescribing patterns were lower for those treated at

(A)



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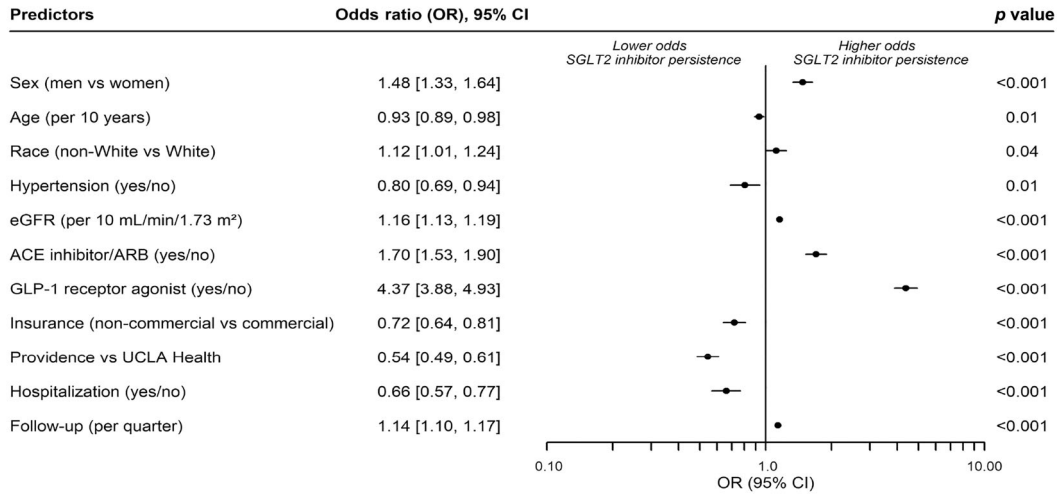

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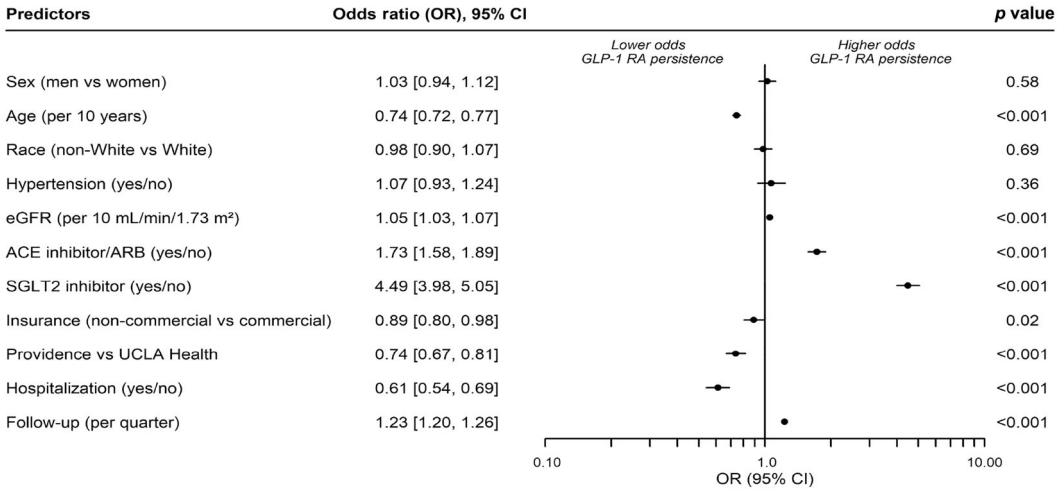

FIGURE 2 (A) Forest plot of predictors after multivariable modelling of prescribing persistence ≥90 days for ACE inhibitor/ARB in diabetes and CKD, 2019-2020. (B) Forest plot of predictors of prescribing persistence ≥90 days for SGLT2 inhibitors in diabetes and CKD, 2019-2020 (N = 36 127). (C) Forest plot of prescribing persistence ≥90 days of GLP-1 receptor agonists in diabetes and CKD, 2019-2020. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; SGLT, sodium-glucose cotransporter; SGLT2, sodium-glucose cotransporter 2; UCLA, University of California Los Angeles Health.

Providence versus UCLA Health. Conversely, higher eGFR and longer follow-up time predicted GDMT persistence.

Currently, GDMT includes a traditional standard of care, an ACE inhibitor/ARB, along with an SGLT2 inhibitor and/or a GLP-1 receptor agonist. These medications, originally approved as glucose-lowering agents, are now recognized for their kidney and heart protective actions independent of glycaemic actions.[4] Unlike previous studies, the present study is distinguished by reporting both baseline prescribing patterns for GDMT as well as persistent prescribing patterns for at least 90 cumulative days.[3,14–17,23] Persistence in prescribing GDMTs is essential as they require ongoing use to be effective, and a call to action of an unmet need. Although prescriber characteristics or precise reasons for medication initiation or discontinuation are not captured in real world data from EHR, barriers contributing to the low GDMT prescribing may include high drug costs, side effects (e.g. hyperkalaemia, eGFR dip, or cough with an ACE inhibitor/ARB), polypharmacy (ACE inhibitor/ARB combined with an SGLT2 inhibitor or GLP-1 receptor agonist and other medications), burden and complexity of care, low frequency of contact with health systems and lack of post-hospitalization follow-up.[31–33] A recent study from the Veterans Administration including a cohort of 141 252 patients with CKD (42.5% with diabetes) reported that ACE inhibitor/ARB medications were interrupted for at least 14 days in >95% of patients, and 39% did not restart these medications within 6 months.[34] Importantly, ACE inhibitor/ARB discontinuation was associated with higher risk of death and kidney failure that increased in a graded fashion with duration of drug discontinuation.[34]

Lack of commercial health insurance as primary coverage was associated with lower prescribing patterns of GDMT and predicted lack of persistence for at least 90 days across the spectrum of therapeutic agents for diabetes and CKD. Clinical care at Providence was also associated with lower odds for being prescribed GDMT compared with UCLA Health, although absolute rates of SGLT2 inhibitor and GLP-1 receptor agonist prescriptions were extremely low in both systems. Providence provides care in geographically dispersed communities with many rural and underserved areas across five western states. In addition, Providence has a low proportion of patients with commercial insurance as the primary payer (19.8%), and not infrequently, patients with no (13%) or unknown health insurance (3.8%). In contrast, UCLA Health cares for more commercially insured patients (38.8%) and essentially none with no or unknown health insurance status in an urban area. Furthermore, UCLA Health cares for high proportions of racial and ethnic minority groups who are also disproportionately affected by diabetes, CKD and other comorbidities.[35,36] Greater persistence of GDMT prescribing in these groups is a step in the right direction compared with earlier reports of lower use in racial and ethnic minority groups.[20,35]

GDMT persistence was predicted by longer follow-up time and higher eGFR. In this contemporary cohort, ACE inhibitor/ARB prescriptions persisted despite hospitalization representing progress in maintaining therapy with acute illness. On the other hand, the likelihood of persistence with SGLT2 inhibitors and GLP-1 receptor agonists dropped significantly with hospitalization. Men were more likely to be prescribed an ACE inhibitor/ARB or an SGLT2 inhibitor than women. These prescribing trends could be related to perceptions about side effect risks in women such as reproductive concerns with an ACE inhibitor/ARB or genital mycotic infections with an SGLT2 inhibitor.[37,38] Persistent prescribing rates of an ACE inhibitor/ARB or an SGLT2 inhibitor was also associated with prescribing a GLP-1 receptor agonist and MRA, suggesting that those who have access to GDMT may be prescribed multiple agents supporting cardiometabolic health. Nevertheless, potential nephrotoxins (e.g. NSAIDs and PPIs) were also more likely to be prescribed to ACE inhibitor/ARB users.

Our observations point to several key strategies for delivering GDMT more equitably to patients with diabetes and CKD. Health policy change in the United States should assure adequate insurance coverage to eliminate differential access to therapies.[33] Hospitalizations provide a window of opportunity to apply GDMT and to schedule timely follow-up visits for medication management that encourages persistent prescribing and use. CKD detection, particularly increased rates of albuminuria testing, and sustainable multidisciplinary models are needed to deliver GDMT at the opportune time of early CKD in diabetes. Furthermore, coordinated care and co-management by clinical teams have proven to increase GDMT use in high-risk populations.[6,9] As access to care, including specialty services, is a large unmet need in underserved regions.[33] the collaborative strategy is particularly relevant for high-risk groups, particularly for disadvantaged populations with diabetes and CKD.[7–9,36,39] To deliver optimal care for diabetes and CKD regardless of location or patient age, education of patients and clinicians is necessary along with readily available technology for remote clinical visits to help increase therapeutic adherence.[40]

Limitations of this study include the use of retrospective observations, missing data and miscoding in the EHR, inability to discern different levels of medication benefit options with different Medicare Advantage plans and Medicaid in different states, and while SGLT2 inhibitors and GLP-1 receptor agonists have been approved for several years, most formal clinical guidelines recommending their use were published during the 2020-2022 time period. Despite these limitations, CURE-CKD has several strengths including a large and diverse population, curated patient-level data with clinical characteristics, vital signs, laboratory values and longitudinal prescription records. To address the limitations inherent in EHR data, we defined diabetes by laboratory tests of haemoglobin A1c and blood glucose, prescriptions for glucose-lowering agents, and administrative codes.[23,24] We could not specifically classify diabetes as type 1 or type 2 or by duration because of the limitations of misclassification and missingness in clinical records. However, as most people with diabetes mellitus have type 2 diabetes (≥95%),[1] and an SGLT2 inhibitor or a GLP-1 receptor agonist was only recommended for type 2 diabetes during the study timeframe,[4] the present analyses will be dominated by these individuals. Similarly, CKD was identified by at least two measurements of eGFR, or albuminuria or proteinuria, or an administrative code for CKD with a confirmatory laboratory test. However, UACR/UPCR values were missing in over half of patients with diabetes and CKD. Therefore, a sensitivity analysis of those with these measurements

was conducted and yielded an overall similar model with the addition of macroalbuminuria as a predictor for ACE inhibitor/ARB prescriptions, supporting our main analysis as a reasonable assessment of GDMT in patients with diabetes and CKD. Finally, while CURE-CKD has representation from populations treated at two health systems serving five western states, it did not include other US regions.

In conclusion, GDMT prescribing of an ACE inhibitor/ARB, a SGLT2 inhibitor, or a GLP-1 receptor agonist was suboptimal and waned quickly in patients with diabetes and CKD treated in contemporary US health systems. Under-prescribing and lack of persistent prescribing for GDMT was associated with not having commercial health insurance as the primary payer and type of health system. Adequate insurance coverage and equitable access to care, including ongoing reassessment of UACR/UPCR, are important strategies for delivery of GDMT to patients with diabetes and CKD.

AUTHOR CONTRIBUTIONS

All authors met the International Committee of Medical Journal Editors criteria for authorship for the article. SBN and KRT led project development from concept through data acquisition, curation, analyses, interpretation and drafting the manuscript. KBD, RZA, CRJ, LMK and KCN contributed to data acquisition, curation, analyses and drafting the manuscript. STF, SXK, JJN and RS provided feedback on the manuscript.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions and would require a data use agreement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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