Three Sides to the Story: Adherence Trajectories During the First Year of SGLT2 Inhibitor Therapy Among Medicare Beneficiaries

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

We aimed to understand the factors associated with sodium–glucose cotransporter 2 inhibitor (SGLT2i) adherence and longitudinal adherence trajectories in older adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Using Medicare claims data (April 2013–December 2017), we identified 83,675 new SGLT2i users ≥66 years old with type 2 diabetes. We measured SGLT2i adherence as the proportion of days covered (PDC) during the first year of SGLT2i therapy. We used linear regression to assess the association between baseline covariates and PDC. Then we used group-based trajectory modeling to identify distinct longitudinal SGLT2i adherence groups and used a multivariable logistic regression model to examine the association between baseline covariates and membership in these adherence groups.

RESULTS

Unadjusted mean PDC was 63%. Previous adherence to statins had the strongest positive association with PDC (regression coefficient 6.00% [95% CI 5.50, 6.50]), whereas female sex (−5.51% [−6.02, −5.00]), and Black race/ethnicity (−5.06% [−6.03, −4.09]) had the strongest negative association. We identified three adherence trajectory groups: low (23% of patients, mean PDC 17%), moderate (32%, mean PDC 50%), and high (45%, mean PDC 96%) adherence. More patients in the high adherence group were previously adherent to statins (odds ratio 1.43 [95% CI 1.39, 1.48]), and more women (1.28 [1.23, 1.32]) and Black patients (1.31 [1.23, 1.40]) were in the low adherence group.

CONCLUSIONS

In a large population of older patients with type 2 diabetes, 45% were highly adherent during the first year of SGLT2i treatment. Female sex and Black race/ethnicity were most strongly associated with low adherence.

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are oral diabetes medications that reduce the risk of atherosclerotic cardiovascular events, hospitalization for heart failure, end-stage kidney disease, and death in older adults with type 2

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diabetes and comorbidities that increase risk of these conditions (1–5). The latest American Diabetes Association guidelines recommended that SGLT2i be considered one of the first medications to be added to metformin for further blood glucose lowering (6). As such, SGLT2i are becoming widely used by older adults (7,8). Although SGLT2i confer many clinical benefits, these medications can be associated with adverse events and are costly (7–10). It is critical to understand factors related to adherence to these medications to reduce the costs associated with medication nonadherence (7,8).

The first SGLT2i was approved for use in the U.S. in 2013 (9). Despite increasing SGLT2i use, only two major studies have examined adherence and persistence patterns of real-world patients taking SGLT2i for type 2 diabetes (9,10). These studies focused on comparing SGLT2i adherence versus other diabetes treatment adherence in two populations, from a U.S. commercial claims database and an Australian pharmacy benefits database. In both studies, investigators found that a considerable portion of SGLT2i users are nonadherent (9,10). Adherence to SGLT2i may be particularly important for older adults, who have a high prevalence of atherosclerotic cardiovascular events, hospitalization for heart failure, and end-stage kidney disease (7,8). All of these may be prevented or improved with SGLT2i (7,8).

We built on this limited but emerging body of literature to understand the factors associated with SGLT2i adherence and trajectories of SGLT2i adherence in older patients with type 2 diabetes using group-based trajectory modeling (11–14).

RESEARCH DESIGN AND METHODS

Data Source, Study Cohort, and Drug Exposure

We performed a population-based, new-user cohort study using Medicare Fee-for-Service data from Parts A (inpatient coverage), B (outpatient coverage), and D (prescription benefits). Medicare is a nationwide U.S. federal health insurer for ~50 million patients primarily aged 65 years and older. Medicare claims data include information on dates and place of service; ICD-9, Clinical Modification (ICD-9-CM) and ICD-10, Clinical Modification (ICD-10-CM) codes; Current Procedural Terminology, Fourth Edition (CPT-4), codes; provider type; the National Drug Code; and prescription drug dispensing dates and days' supply.

The Institutional Review Board of Mass General Brigham approved the study. A licensing agreement with the Centers for Medicare and Medicaid Services was in place.

We included patients aged 66 years and older who initiated an SGLT2i, i.e., canagliflozin, dapagliflozin, or empagliflozin, between 1 April 2013 and 31 December 2017. The cohort entry date was the date of the first SGLT2i prescription. We required patients to be continuously enrolled in Medicare Parts A, B, and D for 1 year prior to and 1 year after the index SGLT2i prescription (see Supplementary Fig. 1). Patients must have had a documented diagnosis code for type 2 diabetes in the year prior to starting treatment with an SGLT2i. Patients were excluded if they had type 1 diabetes, cancer, end-stage kidney disease, HIV, or a nursing home admission during the year prior to the cohort entry date. Because previous medication adherence is likely associated with future adherence (13,15), we required all patients to have one or more prescriptions filled for an ACE inhibitor (ACEi), angiotensin receptor blocker (ARB), metformin, or a statin so that we could account for adherence to previous medications in our model (Supplementary Fig. 2). We began measuring adherence on the day of cohort entry and continued for 1 year. For each patient, we measured a composite adherence score over the full year of follow-up, as well as monthly adherence scores, in twelve 30-day increments.

Study Outcomes

We measured SGLT2i medication adherence as the proportion of days covered (PDC) using pharmacy claims. The numerator included all days that a patient had any SGLT2i on hand, per pharmacy dispensing data. The denominator included the total follow-up time when the patient contributed; this would be 365 days or the number of days the patient was alive during the follow-up (Supplementary Fig. 2).

To measure the PDC numerator, we created a supply diary for each patient that indicated whether each day in a given period was covered by an SGLT2i, based on the dispensing date and days' supply. Each supply diary began on the date of cohort entry and ended 1 year from the index date. To measure the denominator, we removed the days when a patient was not at home (i.e., when the patient was in a hospital, skilled nursing facility, or nursing home) from the supply diary. Each supply diary yielded a composite continuous adherence score and monthly adherence scores for each patient (in 30-day periods) (11–15). The monthly PDC values (continuous scale) were used to identify groups of patients with distinct longitudinal prescription filling patterns during the first year of therapy (11–15).

Covariates

We measured covariates during the 1 year prior to and including the date of cohort entry. We selected covariates that we hypothesized to be related to SGLT2i adherence based on previous adherence studies of diabetes (9,10, 16,17) and cardiovascular medications (11–15,18). Covariates potentially associated with nonadherence were grouped into patient factors, medication-specific factors, and system-level factors (19). We selected several covariates within each category. Patient factors included demographics (age, sex, and race/ethnicity), comorbidities, adherence to previous medications, and health care use (19). Patients were considered adherent to previous medications of interest if they had an overall PDC $\geq$80% in the year prior to cohort entry; this is the most commonly used adherence cut point (11–15). Medication-specific factors included the number and type of prescriptions filled in the previous year (19). System factors included dual Medicare and Medicaid enrollment, variables related to medication cost, and low-income subsidy for the index SGLT2i prescription (19). To address potential confounding by frailty and comorbidity, we included a claims-based frailty index (20) and a claims-based comorbidity index (21) in the model. We identified covariates through ICD-9 or ICD-10 diagnosis or procedure codes, CPT-4 codes, and National Drug Code (pharmacy claims). A complete list of baseline characteristics can be found

in Table 1; see Supplementary Table 1 for associated codes.

Statistical Analysis

We report number and percentages of binary baseline characteristic and means and SDs of continuous baseline characteristics. We used linear regression to assess the association between baseline covariates (see Table 2 for the full list) and PDC over the follow-up period. We interpreted the regression coefficients and 95% CI for each covariate as the estimated percent change in PDC (scale: 0–100%) for every one-unit change in the variable.

We used group-based trajectory modeling to identify patient membership in adherence groups during the first year of therapy (11–15). Adherence is a dynamic behavior that changes over time, and these models can capture these fluctuations within large populations (14). Specifically, we modeled the 12 monthly adherence scores from supply diaries in linear group–based trajectory models (PROC TRAJ [a free downloadable add-on package to SAS, version 9.4; SAS Institute, Cary, NC]). These models include all available monthly adherence data to assign patients to an adherence group for which their probability of membership is the highest (11–14,18). In line with other studies, we assumed a censored normal distribution (11–14,18). We considered multiple models, varying the number of groups from two to six, and selected the one model that had the lowest Bayesian information criterion value, resulted in groups populated by a percentage of patients >5%, had distinct patterns, and resulted in groups where patients had a high probability of being assigned to the group that represented their unadjusted PDC (11–14). The final output of the model included the model's estimated average trajectory in each group and the actual adherence trajectory among group members.

Finally, for each identified adherence trajectory group, we used a multivariable logistic regression model estimating the probability of membership in one adherence group compared with the other groups conditional on baseline covariates (11–15). For each covariate, we estimated the odds ratio (OR) and 95% CI of membership in a specific group compared with the other groups holding all other variables constant.

RESULTS

Study Cohort and Patient Characteristics

After applying the inclusion and exclusion criteria, we identified 83,675 new SGLT2i users (Supplementary Fig. 2). Patients had a mean (SD) age of 72.00 (5.17) years, 15% of patients were frail (20), and patients had a mean combined comorbidity score of 0.98 (1.81), which is associated with a <10% risk of mortality within 1 year (21). Approximately one-half of patients were female, and 81% were White. The proportion of patients with a PDC ≥80% for ACEi or ARB, metformin, or statin in the year prior to cohort entry ranged from 48% to 56%. Patients were taking an average of 14 unique medications and had a high burden of diabetes-related comorbidities. In addition to an SGLT2i, patients were frequently taking metformin (80%), a sulfonylurea (53%), a dipeptidyl peptidase 4 inhibitor (44%), and insulin (27%). Approximately one-half of patients were connected enough to the health system to receive preventive care in the year before cohort entry, given they had at least one code for a bone mineral density screening, colon cancer screening, prostate cancer screening, mammography, or vaccination for influenza or pneumonia (Table 1).

Covariates Associated With SGLT2i Adherence

The unadjusted mean (SD) SGLT2i PDC was 63% (35%), with a median PDC of 74% (interquartile range 25–100). A total of 45% of patients had a PDC ≥80%.

We identified 27 covariates that were significantly associated with SGLT2i adherence (see Table 2). The patient factors (19) that had the strongest positive association with SGLT2i adherence were previous statin (6%) or metformin (4%) adherence, Asian versus White race/ethnicity (4%), and other versus White race/ethnicity (3%). Other factors that were significantly, though less strongly, associated included previous ACEi or ARB adherence, dementia, chronic kidney disease stages 1–2, hyperlipidemia, and having at least one endocrinologist or internist visit in the previous year.

The patient factors that had the strongest negative association with SGLT2i adherence were female versus male sex (−6%), Black versus White race/ethnicity (−5%), Hispanic versus White race/ethnicity (−4%), and anxiety (−3%). Other factors that were significantly, though less strongly, associated included increasing age, increasing frailty, atherosclerotic cardiovascular disease, chronic kidney disease stages 3–5, hyperglycemia, hypertension, and having at least one nephrologist visit in the previous year.

The medication-specific factor (19) that was positively associated with SGLT2i adherence was filling more unique prescriptions in a given month (e.g., filling nine prescriptions at the pharmacy every month rather than eight prescriptions). The medication-specific factor that was negatively associated with SGLT2i adherence was taking a greater number of daily medications (categorical variable with three levels [0–4, 5–10, and 11+]. The model reports a coefficient for a 1 level increase from one category to the next).

The system-level factors (19) that had the strongest positive associations with SGLT2i adherence were dual enrollment in Medicare and Medicaid (3%) and a higher index co-pay for SGLT2i (2%). A higher low-income subsidy for the index SGLT2i was significantly though less strongly associated with adherence. The system-level factor that was negatively associated with SGLT2i adherence was higher total co-pays for non-SGLT2i prescriptions (Table 2).

Adherence Trajectories

Based on the criteria mentioned in RESEARCH DESIGN AND METHODS, we identified a three-group trajectory model (11,14). (See Supplementary Table 2 for model details.) The three groups included the following: *1*) patients with low adherence during the first year of therapy (23% of all patients; mean [SD] PDC 17% [14%]), *2*) patients with moderate adherence (32% of all patients; mean PDC 50% [22%]), and *3*) patients with near-perfect adherence, termed the high adherence group (45% of all patients; mean PDC 96% [9%]) (Fig. 1).

The low adherence group included patients who filled their initial prescription for an SGLT2i but who, on average, filled few to no additional prescriptions. This group included proportionally more

Table 1—Characteristics of new SGLT2i users with continuous Medicare enrollment (*N* = 83,675)

	Frequency
Patient factors	
Demographics	
Age, mean (SD)	72.00 (5.17)
Claims-based frailty index, *n* (%)	
Nonfrail: <0.15	15,765 (18.84)
Prefrail: 0.15–0.24	55,057 (65.80)
Frail: ≥0.25	12,853 (15.36)
Combined comorbidity index, mean (SD)	0.98 (1.81)
Female, *n* (%)*	42,107 (50.32)
Race/ethnicity, *n* (%)*	
White	68,050 (81.33)
Black	5,515 (6.59)
Asian	3,733 (4.46)
Hispanic	2,604 (3.11)
North American Native	294 (0.35)
Other	3,479 (4.16)
Diabetes-related comorbidities	
Atherosclerotic cardiovascular disease, *n* (%)	36,276 (43.35)
Chronic kidney disease, *n* (%)	
Stages 1–2	3,278 (3.92)
Stages 3–5	6,694 (8.00)
Diabetic nephropathy, *n* (%)	8,401 (10.04)
Diabetic neuropathy, *n* (%)	21,724 (25.96)
Diabetic retinopathy, *n* (%)	9,572 (11.44)
Hyperglycemia, *n* (%)	4,357 (5.21)
Hypoglycemia, *n* (%)	6,079 (7.27)
Previous medication adherence†	
Taking ACEi or ARB, mean (SD)	69,067 (82.54)
Adherent to ACEi or ARB, *n* (%)	47,166 (56.37)
Taking metformin, mean (SD)	67,837 (80.24)
Adherent to metformin, *n* (%)	40,166 (47.51)
Taking statin, mean (SD)	67,540 (79.89)
Adherent to statin, *n* (%)	41,223 (49.27)
Adherence-related comorbidities, *n* (%)	
Anxiety	8,630 (10.31)
Delirium or psychosis	1,781 (2.13)
Dementia	3,806 (4.55)
Depression	11,026 (13.18)
Drug or alcohol use	1,548 (1.85)
Other comorbidities, *n* (%)	
Heart failure	8,597 (10.27)
Hyperlipidemia	76,032 (90.87)
Hypertension	77,771 (92.94)
Nonatherosclerotic cardiovascular diseases	15,416 (18.42)
Health care use, *n* (%)	
Cardiologist visit in previous year	37,083 (44.32)
Endocrinologist visit in previous year	18,091 (21.62)
Internist visit in previous year‡	75,533 (90.27)
Nephrologist visit in previous year	8,343 (4.59)
Hospitalized in previous year	8,880 (10.61)
Preventive health procedure code in previous year§	41,747 (49.89)
Medication-specific factors	
Medication count	
Unique medications filled in previous year, mean (SD)	14.05 (6.28)
0–4 medications, *n* (%)	999 (1.19)
5–10 medications, *n* (%)	25,835 (30.88)
11 or more medications, *n* (%)	56,841 (67.93)
Unique prescriptions filled in previous year, mean (SD)	55.40 (39.17)
Cardiovascular medications, *n* (%)	
β-Blockers	40,716 (48.66)
Calcium channel blockers	28,222 (33.73)
Loop diuretics	14,500 (17.33)
Thiazide diuretics	12,715 (15.20)

Continued on p. 608

Table 1—Continued

	Frequency
Diabetes medications, *n* (%)	
DPP-4i	37,218 (44.48)
GLP-1RA	12,458 (14.74)
Insulins	22,419 (26.52)
Meglitinides	2,762 (3.27)
Sulfonylureas	44,552 (53.24)
Thiazolidinediones	10,733 (12.83)
Other chronic medications, *n* (%)	
Antiplatelets	14,607 (17.46)
Antidepressants	23,219 (27.72)
Thyroid medications	17,009 (20.33)
System-level factors	
Medication cost‖	
Dual status, Medicare and Medicaid, *n* (%)	16,508 (19.73)
Ratio of brand-name to generic diabetes medications, mean (SD)¶	0.47 (0.99)
Ratio of brand-name to generic medications, mean (SD)¶	1.03 (0.05)
Medication cost, mean (SD)‖	
Index SGLT2i co-pay (USD)	71.22 (92.81)
Index SGLT2i low-income subsidy (USD)	53.25 (152.15)
Total co-pays in previous year (USD)	1,033.61 (1,098.09)

DPP-4i, dipeptidyl peptidase 4 inhibitors. *Sex and race/ethnicity variable taken directly from Medicare data input. Other race/ethnicity includes race/ethnicity indicated specially as "other" or as unknown. †Previous medication adherence was measured using the PDC over the 365-day covariate assessment period, with a ≥80% cut point for adherent vs. not. ‡Included carrier claims line provider specialty codes: general practice, family practice, and internal medicine. These are distinct from the values included in the cardiologist, endocrinologist, and nephrologist covariates. §Preventive health procedure codes included codes for bone mineral density screening, colon cancer screening, prostate cancer screening, mammography, or vaccination for influenza or pneumonia. ‖Medication cost standardized to USD in 2017 (end of study period) based on inflation rates. ¶The ratio of brand-name to generic medications is the total count of prescriptions that a patient fills for brand-name medications divided by the total count of prescriptions filled for generic medications.

female patients, patients of Black race/ethnicity, and patients with anxiety. The moderate adherence trajectory group included patients who, on average, filled one to two additional prescriptions in the first 6 months of therapy but had a gradual decline in adherence over the subsequent 6 months. This group had few notable differences from the low and high adherence groups; however, the moderate group had the highest index SGLT2i co-pay (mean [SD] USD 80.83 [101.84] vs. 61.36 [68.50] and 69.44 [96.08], respectively). The high adherence group included patients who, on average, had near perfect adherence throughout the year. This group included proportionally more patients of Asian and other race/ethnicity, patients with previous medication adherence, patients enrolled in Medicaid, and patients with a higher low-income subsidy amount for the index SGLT2i (Supplementary Table 3).

Association Between Covariates and Trajectory Group Membership

The above proportional differences were consistent with observed associations between covariates and adherence group membership (Table 3). The strongest associations across the three models were for previous adherence to statins (OR for high adherence 1.43 [95% CI 1.39, 1.48]), Black race/ethnicity (OR for low adherence 1.31 [1.23, 1.40]), and female sex (OR for low adherence 1.28 [1.23, 1.32]) (Supplementary Table 3).

CONCLUSIONS

In a large population-based study including nearly 84,000 older patients with type 2 diabetes who initiated SGLT2i, the overall unadjusted mean SGLT2i PDC was 63%, and only 45% of patients were adherent during the first year of therapy, as measured by an overall PDC of ≥80%. Baseline adherence to metformin and statins was consistently associated with high adherence, while female sex and Black race/ethnicity were consistently associated with low adherence. Our work adds to the literature in three key ways: This is the first study to examine longitudinal SGLT2i adherence, rather than prescription rates (8), in older adults. We examined longitudinal adherence patterns using trajectory analyses in the first year of therapy, a novel method that illustrates dynamic changes and fluctuations in adherence over time (14). Finally, we evaluated what factors may be associated with adherence to SGLT2i among older adults and how those factors may be associated with adherence trajectory.

Our patients' SGLT2i adherence was somewhat lower than in other studies (9,10). In an Australian national pharmacy database study, patients had a mean SGLT2i PDC of 79%, and 66% of patients had a PDC ≥80% in their first year of therapy (10). Similarly, in a U.S. commercial health care database study, 61% of patients had a PDC ≥80% in their first year of therapy (9). Of note, our patients were older than most individuals included in these studies and were receiving Medicare fee-for-service rather than commercial insurance, both of which may have driven the lower SGLT2i adherence rates in our population.

Our results appear more aligned with findings from studies assessing adherence to glucagon-like peptide 1 receptor agonists (GLP-1RA), which are injectable agents often prescribed for patients with

Table 2—Linear regression model for factors associated with medication adherence to SGLT2i during the first year of therapy (*N* = 83,675)

	Change in PDC (%)	95% CI
Intercept	85.84	81.98, 89.70
Patient factors		
5-year increase in age	−1.35	−1.59, −1.11
Increase in frailty category	−2.22	−2.76, −1.68
Combined comorbidity index over previous year	−0.04	−0.23, 0.156
Female vs. male sex*	−5.51	−6.02, −5.00
Black vs. White race/ethnicity*	−5.06	−6.03, −4.09
Asian vs. White race/ethnicity*	4.07	2.85, 5.30
Hispanic vs. White race/ethnicity*	−3.91	−5.34, −2.48
North American Native vs. White race/ethnicity*	−2.35	−6.30, 1.61
Other race/ethnicity vs. White race/ethnicity*	3.24	2.05, 4.42
Previous ACEi or ARB adherence†	2.33	1.82, 2.83
Previous metformin adherence†	4.09	3.60, 4.59
Previous statin adherence†	6.00	5.50, 6.50
Anxiety	−3.09	−3.91, −2.26
Delirium or psychosis	0.63	−1.07, 2.33
Dementia	2.07	0.87, 3.27
Depression	0.43	−0.33, 1.18
Drug or alcohol use	−0.36	−2.12, 1.41
Atherosclerotic cardiovascular disease	−1.52	−2.10, −0.93
Chronic kidney disease, stages 1–2	1.47	0.18, 2.77
Chronic kidney disease, stages 3–5	−2.40	−3.45, −1.34
Diabetic nephropathy	−0.63	−1.51, 0.24
Diabetic neuropathy	−0.54	−1.11, 0.03
Diabetic retinopathy	0.24	−0.51, 0.98
Hyperglycemia	−1.16	−2.22, −0.10
Hypoglycemia	−0.58	−1.49, 0.34
Heart failure	−0.67	−1.60, 0.25
Hyperlipidemia	0.96	0.12, 1.80
Hypertension	−2.06	−3.04, −1.09
Nonatherosclerotic cardiovascular diseases	0.25	−0.44, 0.94
At least one cardiologist visit in previous year	−0.57	−1.17, 0.02
At least one endocrinologist visit in previous year	0.97	0.37, 1.56
At least one internist visit in previous year‡	1.11	0.31, 1.92
At least one nephrologist visit in previous year	−1.38	−2.67, −0.09
At least one hospitalization in previous year	−0.10	−0.95, 0.75
At least one screening or vaccine in previous year§	0.39	−0.09, 0.87
Medication-specific factors		
One additional prescription filled per month	0.59	0.50, 0.69
Increase in number of medications category	−1.98	−2.54, −1.41
System-level factors		
Dual status	3.31	2.37, 4.26
One quartile increase in SGLT2i index co-pay‖	2.10	1.77, 2.44
One quartile increase in SGLT2i low-income subsidy‖	0.17	0.14, 0.20
One quartile increase in total co-pays	−1.62	−1.94, −1.30

*Sex and race/ethnicity variable taken directly from Medicare data input. Other race/ethnicity includes race/ethnicity indicated specially as "other" or as unknown. †Previous medication adherence was measured using the PDC over the 365-day covariate assessment period, with a ≥80% cut point for adherent vs. not. ‡Included carrier claims line provider specialty codes: general practice, family practice, and internal medicine. These are distinct from the values included in the cardiologist, endocrinologist, and nephrologist covariates. §Preventive health procedure codes included codes for bone mineral density screening, colon cancer screening, prostate cancer screening, mammography, or vaccination for influenza or pneumonia. ‖Medication cost standardized to USD in 2017 (end of study period) based on inflation rates.

characteristics similar to characteristics of those prescribed SGLT2i. Among Medicare enrollees who initiated treatment with GLP-1RA, only 37% had a PDC ≥80% during the first 6 months of therapy (17). In a U.S. single-payer health insurance database study, 61% of new and persistent GLP-1RA users had a PDC ≥80% over 6 months (16). In a similar study in a U.S. commercial database, 51% of new GLP-1RA users had a PDC ≥80% during the first year of therapy (22).

Our group-based trajectory analysis showed patterns similar to those of other adherence trajectory analyses (23). In most analyses investigators identified one group with near-perfect adherence, one with a rapid adherence decline, and several additional (typically 1–3) groups in between (23). We identified three adherence trajectory groups: low, moderate, and high adherence. As many adverse effects occur early in therapy, adverse effects after the initial

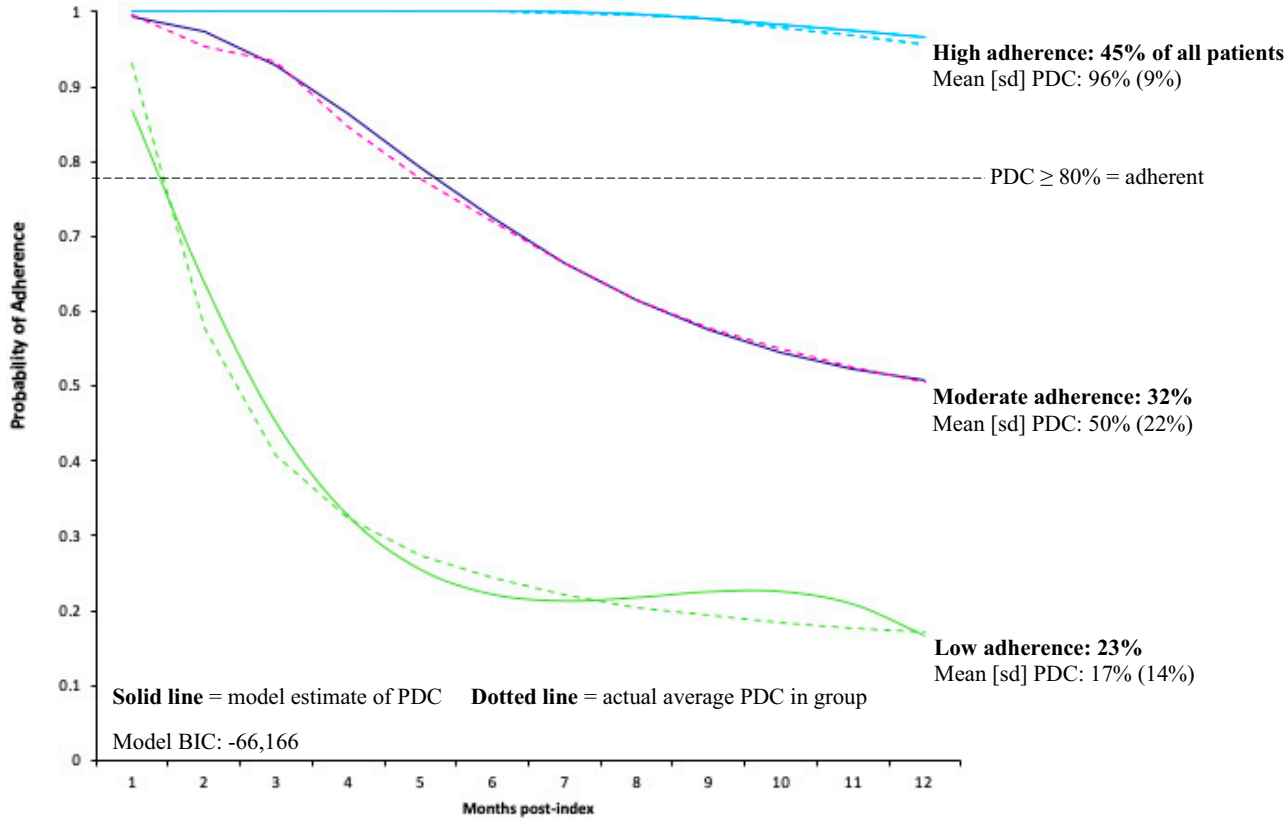

Figure 1—Adherence trajectories of *N* = 83,675 Medicare beneficiaries over the first year of SGLT2i. Trajectories of adherence to SGLT2i during the first year of therapy among Medicare beneficiaries. The *x*-axis represents time in months since the first SGLT2i prescription was filled. The *y*-axis represents the probability of adherence each month, measured as the PDC on a continuous scale. The dashed line at a probability of 0.8 shows the literature-derived binary cut point for adherent versus not. We identified three trajectories: those with low adherence (23% of all study participants), those with moderate adherence (32%), and those with high adherence (45%). Solid trajectory lines represent the model estimate for PDC, while the dotted trajectory lines represent the actual average PDC of participants within the groups. The model had a Bayesian information criterion (BIC) value of −66,166.

SGLT2i fill may have been related to the low adherence trajectory but were less likely related to the moderate adherence trajectory (23). Future analyses that include clinical or patient-reported data may be able to identify potential factors that affect adherence in the moderate group over the first 6 months of SGLT2i therapy, where we saw trajectories begin to decline.

Similar to other analyses, covariates related to socioeconomic status, comorbidities, frailty, and certain treatment patterns were associated with trajectory group membership (23). These findings can help identify targets for future adherence interventions (23).

The modifiable factor most strongly associated with high SGLT2i adherence was previous medication adherence. In adherence studies based on commercial (15,24) and Medicare data (13), patients who were previously adherent to other chronic medicine regimes were likely to be adherent currently and in the future. In our study, this suggests that targeted efforts to improve adherence to chronic pharmacological treatments, e.g., statins, may improve future adherence. Some adherence interventions address co-payments and subsidies (25,26). In our study, we found that dual status and higher SGLT2i co-pay were positively associated with adherence, whereas higher low-income subsidy amount was not associated. Further research may be able to disentangle the relationship of co-payments, dual Medicare and Medicaid eligibility, and subsidies for higher cost medications for older patients.

The nonmodifiable factors most strongly associated to low SGLT2i adherence were specific racial/ethnic groups and female sex. In our study and others, Black race/ethnicity, Hispanic race/ethnicity, and female sex had negative associations with adherence (13,14,18,27–33). Studies have found that both younger and older female patients are less adherent than male patients (13,14,18,27–33). Authors hypothesize that regardless of age, female patients may be more likely to be balancing factors competing with medication adherence, such as work, family, and caregiving (13,14,18,27–33). For older patients specifically, female patients have been found to more likely be caregivers compared with male patients, which may be negatively associated with adherence (32,33).

Sex may be related to other factors associated with adherence: in a Medicare study of antihypertension medication treatment adherence, overall, female sex was negatively associated with adherence and eligibility for low-income subsidy was positively associated (31). However, female sex and receiving a low-income subsidy were strongly associated with being adherent in both the Black and Hispanic race/ethnicity groups (31). With regard to SGLT2i, a retrospective cohort of commercially insured adults in the U.S. showed that Black and female patients

Table 3—Estimated ORs for the association between patient characteristics and patient trajectory group (*N* = 83,675)

	OR of group membership (95% CI)		
	Low adherence (group 1 [*n* = 19,000, 23%] vs. groups 2 and 3 [*n* = 64,675])	Moderate adherence (group 2 [*n* = 26,497, 32%] vs. groups 1 and 3 [*n* = 57,178])	High adherence (group 3 [*n* = 38,178, 45%] vs. groups 1 and 2 [*n* = 45,497])
Patient factors			
Demographics			
Age	1.05 (1.03, 1.07)	1.02 (1.01, 1.04)	0.95 (0.93, 0.96)
More advanced frailty category	1.12 (1.08, 1.16)	1.02 (0.99, 1.06)	0.91 (0.88, 0.94)
Higher combined comorbidity index over previous year	0.99 (0.98, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)
Female vs. male sex*	1.28 (1.23, 1.32)	1.10 (1.06, 1.13)	0.77 (0.75, 0.78)
Race/ethnicity*			
Black vs. White race/ethnicity	1.31 (1.23, 1.40)	1.11 (1.04, 1.18)	0.73 (0.68, 0.77)
Asian vs. White race/ethnicity	0.77 (0.70, 0.85)	1.04 (0.96, 1.13)	1.13 (1.05, 1.21)
Hispanic vs. White race/ethnicity	1.23 (1.11, 1.35)	1.22 (1.12, 1.33)	0.72 (0.66, 0.79)
North American Native vs. White race/ethnicity	0.97 (0.73, 1.27)	1.35 (1.06, 1.72)	0.77 (0.61, 0.98)
Other race/ethnicity vs. White race/ethnicity	0.90 (0.83, 0.98)	0.93 (0.86, 1.00)	1.14 (1.06, 1.22)
Previous medication adherence†			
Adherent to ACEi or ARB	0.89 (0.86, 0.92)	0.93 (0.90, 0.96)	1.17 (1.14, 1.21)
Adherent to metformin	0.79 (0.76, 0.82)	0.90 (0.87, 0.93)	1.30 (1.26, 1.33)
Adherent to statin	0.72 (0.70, 0.75)	0.86 (0.84, 0.89)	1.43 (1.39, 1.48)
Adherence-related comorbidities			
Anxiety	1.20 (1.13, 1.27)	1.03 (0.98, 1.08)	0.85 (0.81, 0.89)
Delirium or psychosis	0.95 (0.84, 1.07)	0.99 (0.89, 1.11)	1.05 (0.95, 1.16)
Dementia	0.94 (0.87, 1.02)	0.92 (0.85, 0.99)	1.12 (1.05, 1.21)
Depression	0.94 (0.89, 0.99)	1.03 (0.98, 1.08)	1.02 (0.97, 1.07)
Drug or alcohol use	0.91 (0.80, 1.03)	1.22 (1.10, 1.36)	0.90 (0.81, 1.00)
Diabetes-related comorbidities			
Atherosclerotic cardiovascular disease	1.07 (1.02, 1.11)	1.05 (1.01, 1.09)	0.91 (0.88, 0.95)
Chronic kidney disease, stages 1–2	0.92 (0.84, 1.00)	1.03 (0.95, 1.12)	1.04 (0.96, 1.12)
Chronic kidney disease, stages 3–5	1.02 (0.95, 1.10)	1.03 (0.96, 1.10)	0.97 (0.91, 1.03)
Diabetic nephropathy	1.02 (0.96, 1.09)	1.04 (0.99, 1.10)	0.95 (0.90, 1.00)
Diabetic neuropathy	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)	0.96 (0.93, 0.99)
Diabetic retinopathy	0.97 (0.92, 1.02)	1.04 (0.99, 1.09)	0.99 (0.95, 1.03)
Hyperglycemia	1.04 (0.97, 1.12)	1.02 (0.95, 1.09)	0.96 (0.90, 1.02)
Hypoglycemia	1.01 (0.95, 1.08)	1.05 (0.99, 1.11)	0.95 (0.90, 1.00)
Other comorbidities			
Heart failure	1.03 (0.97, 1.10)	1.03 (0.97, 1.09)	0.96 (0.91, 1.01)
Hyperlipidemia	0.95 (0.90, 1.01)	1.04 (0.99, 1.10)	1.00 (0.96, 1.06)
Hypertension	1.07 (0.99, 1.15)	1.07 (1.00, 1.14)	0.90 (0.85, 0.95)
Nonatherosclerotic cardiovascular diseases	0.97 (0.93, 1.02)	1.00 (0.96, 1.04)	1.03 (0.98, 1.07)
Health care use			
At least one cardiologist visit in previous year	1.00 (0.96, 1.05)	1.04 (1.00, 1.08)	0.96 (0.93, 0.99)
At least one endocrinologist visit in previous year	0.90 (0.86, 0.94)	1.04 (1.00, 1.08)	1.04 (1.01, 1.08)
At least one internist visit in previous year‡	0.94 (0.89, 0.99)	0.98 (0.94, 1.03)	1.06 (1.01, 1.11)
At least one nephrologist visit in previous year	1.04 (0.96, 1.14)	1.04 (0.96, 1.13)	0.93 (0.86, 1.01)
At least one hospitalization in previous year	1.06 (1.00, 1.13)	0.94 (0.89, 0.99)	1.01 (0.96, 1.06)
At least one preventive health procedure code in previous year§	0.98 (0.94, 1.01)	0.98 (0.95, 1.01)	1.04 (1.01, 1.07)
Medication-specific factor: medication count			
Increase in number of medications category	1.02 (0.99, 1.07)	1.13 (1.09, 1.17)	0.89 (0.86, 0.92)
More prescriptions filled in previous year	0.98 (0.98, 0.99)	0.96 (0.95, 0.97)	1.04 (1.04, 1.05)
System-level factor: medication cost‖			
Dual status, Medicare and Medicaid	0.88 (0.82, 0.94)	1.00 (0.94, 1.06)	1.12 (1.06, 1.18)
Higher index SGLT2i co-pay	1.07 (1.05, 1.10)	0.81 (0.80, 0.83)	1.15 (1.13, 1.18)
Higher index SGLT2i low-income subsidy	0.98 (0.97, 0.98)	1.01 (1.00, 1.01)	1.01 (1.01, 1.01)
Higher total co-pays in previous year	1.01 (0.99, 1.03)	1.07 (1.05, 1.09)	0.94 (0.92, 0.95)

*Sex and race/ethnicity variable taken directly from Medicare data input. Other race/ethnicity includes race/ethnicity indicated specially as "other" or as unknown. †Previous medication adherence was measured using the PDC over the 365-day covariate assessment period, with a ≥80% cut point for adherent vs. not. ‡Included carrier claims line provider specialty codes: general practice, family practice, and internal medicine. These are distinct from the values included in the cardiologist, endocrinologist, and nephrologist covariates. §Preventive health procedure codes included codes for bone mineral density screening, colon cancer screening, prostate cancer screening, mammography, or vaccination for influenza or pneumonia. ‖Medication cost standardized to USD in 2017 (end of study period) based on inflation rates.

with low socioeconomic status were less likely to receive SGLT2i in the first place (34).

Some studies suggest that these patterns may be related to social factors or systemic racism (35). While we have included variables that may be related to socioeconomic factors (14,18,28,31) such as low-income subsidy, dual enrollment in Medicaid, and cost variables, many covariates are not directly measurable in Medicare claims data, including primary language (28), income, education level, and labor market status, which have been demonstrated to be associated with statin adherence (36–38). Future research is needed to understand the impact that social and socioeconomic factors may have on adherence to newer diabetes medications and how these relationships may differ based on sex and race/ethnicity (34,38). For example, interventions that target less significant but positive factors, including subsidies or co-payments, may reduce disparities in medication adherence for individuals in racial or ethnic groups often found to have low medication adherence. In the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial, where individuals with a history of a myocardial infarction were randomized to receive preventive cardiac medications for free or for a standard co-payment (25), there was a greater increase in adherence among patients in racial and ethnic minorities compared with White patients (26). Furthermore, patients in racial and ethnic minority groups were significantly less likely to experience a major cardiac event (reduced 35%) and had 70% lower health care spending compared with White patients (26). Authors concluded that lowering co-payments for medications after a myocardial infarction may reduce racial and ethnic disparities in cardiovascular care (26).

This study has limitations. First, claims-based measures of adherence do not identify whether patients actually take their prescriptions or the reasons for nonadherence. Patients in our study may have been instructed to stop SGLT2i treatment or to switch to another diabetes medication for various reasons, including adverse effects. Second, claims do not capture instances where patients pay for prescriptions entirely out of pocket. Our study showed mean (SD) index copayments for SGLT2i of USD 71.22 (92.81) for a 30–90 days' supply and that people who paid more were more adherent. Thus, the possibility of patients paying out of pocket without complete capture may be less of an issue in this study. Third, the associations seen in both of our models were modest, with changes in PDC ranging from 0 to 6% and significant ORs as low as 0.72 and no higher than 1.43 (both for statin adherence). In some instances, these small associations may have appeared to be conflicting; for example, higher numbers of prescriptions filled each month were positively associated with future adherence, while a higher number of daily medicines was negatively associated. In further research, investigators may consider whether $<2\%$ changes in adherence are associated with meaningful clinical effects. In previous studies, a 5% change in adherence was associated with clinical effects (25,39). Fourth, we did not have access to relevant clinical variables including duration of diabetes, hemoglobin A_{1c} values, and BMI, which limited our ability to adjust for diabetes severity, glycemic control, and other risk factors that may affect SGLT2i adherence. Finally, this analysis was completed in adults aged 66 years and older who were new SGLT2i users; these findings may not be generalizable to younger populations with different diabetes and chronic disease state management plans.

Conclusion

Overall, in a large population-based cohort study of 83,675 older adults with type 2 diabetes, only 45% were adherent during the first year of SGLT2i treatment. Baseline adherence to metformin and statins was consistently associated with the higher adherence group, while female sex and Black race/ethnicity were consistently associated with the lower adherence group. Future research is needed for an understanding of the relationship of sex, race/ethnicity, and social and socioeconomic factors with diabetes medication adherence. Interventions may target modifiable and nonmodifiable factors to improve adherence for individuals in groups with low medication adherence.

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