Treatment Modification After Initiating Second-Line Medication for Type 2 Diabetes

David T. Liss, PhD; Manisha Cherupally, MS; Matthew J. O'Brien, MD, MSc; Raymond H. Kang, MA; Cassandra Aikman, MPH; Amisha Wallia, MD, MS; Andrew J. Cooper, MSc; Eleena Koep, MS; Emily D. Parker, PhD, MPH; and Ronald T. Ackermann, MD, MPH

ABSTRACT

OBJECTIVES: To describe changes in antidiabetic medication (ADM) use and characteristics associated with changes in ADM use after initiation of noninsulin second-line therapy.

STUDY DESIGN: Retrospective cohort study.

METHODS: This study analyzed private health plan claims for adults with type 2 diabetes who initiated 1 of 5 index ADM classes: sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), or thiazolidinediones. Analyses evaluated 3 treatment modification outcomes—discontinuation, switching, and intensification—over 12-month follow-up.

RESULTS: Of 82,624 included adults, nearly two-thirds (63.6%) experienced any treatment modification. Discontinuation was the most common modification (38.6%), especially among patients prescribed GLP-1 RAs (50.3%). Switching occurred in 5.2% of patients and intensification in 19.8%. In adjusted analysis, compared with patients prescribed sulfonylureas, discontinuation risk was 7% higher (HR, 1.07; 95% CI, 1.04-1.10) among patients prescribed DPP4is and 28% higher (HR, 1.28; 95% CI, 1.23-1.33) among patients prescribed GLP-1 RAs. Compared with sulfonylureas, all other index ADM classes had higher risks of switching and lower risks of intensification. Younger age group and female sex were both associated with higher risks of all modifications. Compared with index ADM prescription by a family medicine or internal medicine physician, index prescription by an endocrinologist was associated with both lower discontinuation risk and higher intensification risk.

CONCLUSIONS: Most patients experienced a treatment modification within 1 year. Results highlight the need for new prescribing approaches and patient supports that can maximize medication adherence and reduce health system waste.

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Recent research findings have identified metformin as the initial medication choice for 77% of patients starting pharmacotherapy for type 2 diabetes,[1] reflecting treatment patterns largely in accordance with clinical guidelines. However, to achieve long-term glycemic control, most patients ultimately require combination therapy with other antidiabetic medication (ADM) classes.[2] Options for initial second-line ADM after failure of metformin monotherapy are increasing rapidly, with multiple therapeutic classes demonstrating effective glycemic control and cardiovascular and renal benefits.[3-7] However, there is no clinical consensus about which ADM should be used as initial second-line pharmacotherapy in combination with metformin.

Currently, the following 5 noninsulin ADM classes are available when metformin monotherapy is no longer sufficient for glycemic control: sulfonylureas/meglitinides (henceforth, sulfonylureas), dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and thiazolidinediones (TZDs). Practice guidelines direct clinicians to consider multiple factors when selecting a second-line ADM, including the drug's effects on glycemic control,[8] cardiovascular events,[4,9] renal disease progression,[10] and body weight.[11] Patients' preferences based on potential benefits, adverse effects, and medication costs should also be considered.

There are limited data describing patterns of ADM use after failure of metformin monotherapy. One recent national study of adults with type 2 diabetes found that approximately half of patients receiving metformin monotherapy required second-line treatment within 3.4 years, with sulfonylureas being the most common choice.[12] National data on US adults with type 2 diabetes demonstrate the following consistent trends in second-line ADM use over the past 20 years: (1) a large proportional decrease in TZD use, (2) a small reduction in sulfonylurea use, and (3) increases in use of newer medication classes (ie, DPP4is, GLP-1 RAs, and SGLT2is) after introduction to market.[12-14] Although prior research has examined some ADM changes after initiation of second-line therapy,[1,12,15-17] this literature has not examined all types of medication changes from patients' and clinicians' perspectives, namely discontinuing

TAKEAWAY POINTS

Among privately insured adults starting noninsulin second-line therapy for type 2 diabetes, nearly two-thirds (63.6%) experienced any of 3 treatment modification outcomes—discontinuation, switching, and intensification—over a 12-month follow-up.

- Discontinuation was the most common modification (38.6%), followed by intensification (19.8%) and switching (5.2%).
- Patients prescribed sulfonylureas had the lowest adjusted switching risk and the highest adjusted intensification risk.
- Younger age group and female sex were associated with higher risks of all modification outcomes.
- Findings highlight the need to better understand barriers to medication adherence among patients who discontinued treatment to maximize adherence and reduce health system waste.

the second-line ADM (at the behest of either patients or clinicians), switching to a new ADM (after a prescribing clinician's decision to change the pharmacotherapy regimen because of factors like adverse effects or inadequate glycemic control), and intensifying the ADM regimen (presumably due to inadequate glycemic control). Additionally, prior research was not designed to examine predictors of these medication changes. Finally, earlier studies were largely confined to the years before the introduction of newer ADM classes such as SGLT2is.

The current study evaluated data from the period after SGLT2i introduction to address these gaps in the evidence base. Our aims were to (1) describe changes in medication use experienced by patients who initiated different classes of noninsulin second-line ADM therapy and (2) identify patient and provider characteristics that are independently associated with changes in medication use after initiation of second-line therapy.

METHODS

Study Design and Data

This was a retrospective cohort study comparing modifications in diabetes treatment regimen among adults with type 2 diabetes who were initially prescribed 1 of the 5 classes of noninsulin second-line ADMs. As done previously,[13,18,19] our study team used nationwide sources of administrative claims data for privately insured US adults with type 2 diabetes. Data sources included health plan enrollment files, medical inpatient and ambulatory claims, and pharmacy claims between July 2013 and December 2017. Our use of coded, nonidentifiable data was deemed non–human subjects research by Northwestern University's institutional review board.

Study Setting and Inclusion Criteria

The study included adults (18 years or older) who were enrolled in a commercial or Medicare Advantage health plan and initiated an index, second-line ADM prescription between January 1, 2014, and June 30, 2017. Included patients were required to have continuous health plan enrollment for at least 6 months before and 6 months after the date of index medication initiation (ie, the index date). During this 12-month period of continuous enrollment, patients were required to have no change in health plan insurance segment (commercial vs Medicare Advantage) or health plan structure (health maintenance organization [HMO], preferred provider organization [PPO], etc). Each patient's follow-up period lasted up to 12 months after the index date. The **eAppendix Figure** (eAppendix available at **ajmc.com**) provides additional details on dates of data collection and identification of study periods.

Included patients had preexisting type 2 diabetes, defined as 2 or more outpatient diagnosis codes or 1 or more inpatient diagnosis codes for type 2 diabetes at any point before the index date (extending back as far as January 1, 2011). Included patients had at least 1 pharmacy claim for metformin during the 6 months before the index date and a pharmacy claim on the index date for at least a 28-day supply of 1 included index medication.

Patients were excluded if they had 2 or more diagnosis codes for type 1 diabetes, any claims for a nonmetformin ADM before the index date (extending back as far as January 1, 2011), or a pharmacy claim for 2 or more nonmetformin ADMs on the index date. Patients missing data for any variables used in regression analysis were also excluded.

Treatment Modification Outcomes

Study outcomes were defined as time-to-event data to be evaluated in Cox proportional hazards regression models. All included patients were followed after their index dates until experiencing 1 of 4 diabetes treatment modification outcomes: no treatment modification for up to 12 months; discontinuation of the index ADM without replacement with another ADM; switching (discontinuation of the index ADM with replacement by another ADM class); or intensification. We only evaluated each patient's first observed treatment modification; any subsequent modifications were not considered during analysis.

Patients were classified as having no treatment modification if they consistently obtained prescription refills from the index medication class and did not initiate medications from any other ADM classes throughout the follow-up period. As done previously,[20,21] we defined a prescription refill as a pharmacy claim for a subsequent fill in the same ADM class within 60 days after the prior fill was exhausted (based on calculated days' supply). Discontinuation was defined as times when a prescription was exhausted and the patient did not refill a medication from the index medication class or initiate a new medication from another ADM class within 60 days. Switching was defined as discontinuation of the index medication and—within 60 days of exhausting the final index medication fill—initiation of a medication from another index medication class.

Patients met the definition of treatment intensification in 3 ways: (1) doubling (or more) the dose of their index medication from one fill to the next; only patients taking the 4 index medication classes

besides GLP-1 RAs—for which patients often titrate upward to the maximum tolerable dose[22]—were eligible for this form of intensification; (2) starting another index medication class while continuing to refill the index medication; or (3) initiating basal insulin (regardless of whether the index medication continued to be refilled).

Predictor and Covariate Measures

We collected several predictor and covariate measures for each patient at the time of the index date. The primary predictor was a 5-category measure of index medication class (sulfonylureas were the referent group in regression analyses). We also collected measures on patient demographics including age, sex, and US Census region. Because provider characteristics can influence the choice of index medication,[13] we collected data on the type of clinician who prescribed the index medication. Measures of health plan characteristics included insurance segment, consumer-driven health plan (CDHP) enrollment (ie, having a commercial plan with a health reimbursement arrangement or health savings account), and health plan structure. Diabetes-related comorbidity was measured using the Diabetes Complications Severity Index (DCSI) score.[23] For patients with available hemoglobin A_{1c} (HbA_{1c}) data, we evaluated glycemic control prior to the index date using the most recent HbA_{1c} result from the 6-month period preceding the index date (the insurer whose claims were evaluated obtained HbA_{1c} results through data sharing agreements with several individual laboratory vendors; however, HbA_{1c} results were not available for patients whose HbA_{1c} testing was done at laboratories that did not share data with the insurer). To adjust for temporal patterns over time, we also collected the year of the index date.

Statistical Analysis

Statistical analyses were conducted using SAS Viya software (SAS Institute Inc) with $\alpha = .05$. We computed descriptive statistics for baseline characteristics and unadjusted rates of each treatment modification outcome during follow-up.

In adjusted analysis to evaluate differences in the time to each outcome, we estimated multivariable Cox proportional hazards models that account for competing risks. We estimated 3 regression models, 1 for each of the 3 treatment modification outcomes. Each model adjusted for all covariates outlined earlier (with a composite indicator for insurance segment and CDHP enrollment). Our censoring approach followed the cause-specific proportional hazards approach to competing risks analysis.[24,25] Patients were censored at the time of any observed treatment modification, with modifications besides each modeled outcome treated as competing risks (eg, in the model for the discontinuation outcome, patients were censored at the time of switching or intensification). Patients were also censored at the time of health plan disenrollment, any change in insurance segment or health plan structure, or the end of 12-month follow-up.

When reviewing the timing of observed treatment modifications, we identified 1192 patients (1.4% of all included patients) who switched or intensified treatment within 1 week of their index date. Because administrative claims data have inherent limitations that precluded us from identifying the reasons for these rapid treatment modifications, we also conducted a sensitivity analysis omitting these 1192 patients.

RESULTS

A total of 82,624 adults with type 2 diabetes met all inclusion criteria (the **eAppendix Table** presents detailed data on sample size after individual inclusion and exclusion criteria were applied). As shown in **Table 1**, approximately half of included patients received a sulfonylurea as their index medication (42,118; 51.0%); the next most common index medication classes were DPP4is (19,830; 24.0%), SGLT2is (9624; 11.6%), GLP-1 RAs (6707; 8.1%), and TZDs (4345; 5.3%). Most of the included patients were men (54.0%), had a non-Medicare commercial insurance plan (57.0%), and had no diabetes complications (61.5%). Pluralities of patients had their index medication prescribed by a family medicine physician (42.1%), had a point-of-service health plan (which combines elements of HMO and PPO plans) (40.7%), or were aged 65 to 74 years (28.2%). HbA_{1c} data were available for a total of 43,457 patients (52.6%).

The **Figure** presents data on treatment modification outcomes, defined as each patient's first observed treatment modification. As shown in the figure, 63.6% of all patients experienced a treatment modification during follow-up. Discontinuation was by far the most common modification (38.6%). Approximately 1 in 20 (5.2%) patients switched their ADM class, and approximately 1 in 5 (19.8%) intensified treatment. Only 36.4% of included patients did not experience any treatment modifications. By a wide margin, discontinuation was most common among patients initially prescribed GLP-1 RAs (50.3%); for other index medication classes, the proportion of patients who discontinued ranged from 34.2% (TZDs) to 39.5% (DPP4is). Switching was most common among patients initially prescribed DPP4is (8.7%) and least common among patients initially prescribed sulfonylureas (3.0%). Intensification was most common among patients initially prescribed sulfonylureas (23.0%).

Table 2 presents detailed unadjusted results on treatment switching and intensification. Among the 4342 patients who switched ADM classes, switching to a sulfonylurea (1429; 32.9%) was most common, particularly among the 1729 patients who switched after an initial DPP4i prescription (978; 56.6%). Switching patterns varied across other classes; for example, patients with an SGLT2i index medication who switched ADM classes (669) most frequently switched to DPP4is (267; 39.9%). Among the 16,327 patients who experienced 1 of the 3 forms of treatment intensification, the majority intensified by increasing their index medication dose (8559; 52.4%); this form of intensification was especially common among the 9679 participants initially prescribed sulfonylureas who intensified treatment (6602; 68.2%). There were 2112 patients who intensified treatment by initiating basal insulin (12.9%); this form of intensification was proportionally least common among

TABLE 1. Characteristics of Commercial Insurance and Medicare Advantage Enrollees at the Time of the Index Medication

Characteristic	Total, n (%)[a]	Index medication class, n (%)[a]				
		Sulfonylurea	DPP4i	SGLT2i	GLP-1 RA	TZD
n (row %)	82,624	42,118 (51.0)	19,830 (24.0)	9624 (11.6)	6707 (8.1)	4345 (5.3)
Age group in years						
18-44	9800 (11.9)	4133 (9.8)	2172 (11.0)	1622 (16.9)	1488 (22.2)	385 (8.9)
45-54	17,308 (20.9)	7461 (17.7)	4199 (21.2)	2934 (30.5)	1968 (29.3)	746 (17.2)
55-64	21,792 (26.4)	10,065 (23.9)	5506 (27.8)	3190 (33.1)	2026 (30.2)	1005 (23.1)
65-74	23,259 (28.2)	13,841 (32.9)	5277 (26.6)	1557 (16.2)	1060 (15.8)	1524 (35.1)
≥75	10,465 (12.7)	6618 (15.7)	2676 (13.5)	321 (3.3)	165 (2.5)	685 (15.8)
Sex						
Men	44,650 (54.0)	23,413 (55.6)	10,777 (54.3)	5307 (55.1)	2638 (39.3)	2515 (57.9)
Women	37,974 (46.0)	18,705 (44.4)	9053 (45.7)	4317 (44.9)	4069 (60.7)	1830 (42.1)
Prescribing clinician						
Family medicine physician	34,756 (42.1)	17,939 (42.6)	8064 (40.7)	4049 (42.1)	2426 (36.2)	2278 (52.4)
Endocrinologist	4140 (5.0)	1126 (2.7)	1151 (5.8)	728 (7.6)	1015 (15.1)	120 (2.8)
Internal medicine physician	26,443 (32.0)	14,350 (34.1)	6481 (32.7)	2708 (28.1)	1676 (25.0)	1218 (28.0)
Nurse practitioner/physician assistant	8170 (9.9)	3731 (8.9)	2001 (10.1)	1201 (12.5)	900 (13.4)	337 (7.8)
Other	9125 (11.0)	4972 (11.8)	2133 (10.8)	938 (9.7)	690 (10.3)	392 (9.0)
Insurance segment/CDHP						
Commercial, no CDHP	36,745 (44.5)	15,383 (36.5)	9505 (47.9)	6123 (63.6)	4159 (62.0)	1575 (36.2)
Commercial, CDHP	10,359 (12.5)	4783 (11.4)	2298 (11.6)	1729 (18.0)	1048 (15.6)	501 (11.5)
Medicare Advantage	35,520 (43.0)	21,952 (52.1)	8027 (40.5)	1772 (18.4)	1500 (22.4)	2269 (52.2)
Health plan structure						
Health maintenance organization	18,949 (22.9)	10,669 (25.3)	4367 (22.0)	1493 (15.5)	1122 (16.7)	1298 (29.9)
Exclusive provider organization	4388 (5.3)	1921 (4.6)	1075 (5.4)	709 (7.4)	491 (7.3)	192 (4.4)
Indemnity	557 (0.7)	310 (0.7)	146 (0.7)	50 (0.5)	21 (0.3)	30 (0.7)
Point of service	33,641 (40.7)	14,214 (33.7)	8263 (41.7)	5844 (60.7)	3840 (57.3)	1480 (34.1)
Preferred provider organization	4040 (4.9)	2458 (5.8)	884 (4.5)	263 (2.7)	197 (2.9)	238 (5.5)
Other	21,049 (25.5)	12,546 (29.8)	5095 (25.7)	1265 (13.1)	1036 (15.4)	1107 (25.5)
Diabetes Complications Severity Index score						
0	50,807 (61.5)	24,679 (58.6)	11,994 (60.5)	6875 (71.4)	4613 (68.8)	2646 (60.9)
1	15,249 (18.5)	7979 (18.9)	3661 (18.5)	1590 (16.5)	1118 (16.7)	901 (20.7)
2	8988 (10.9)	4977 (11.8)	2247 (11.3)	737 (7.7)	580 (8.6)	447 (10.3)
≥3	7580 (9.2)	4483 (10.6)	1928 (9.7)	422 (4.4)	396 (5.9)	351 (8.1)
Most recent HbA_{1c} level						
<8% (<64 mmol/mol)	19,672 (23.8)	8835 (21.0)	5145 (25.9)	2344 (24.4)	2103 (31.4)	1245 (28.7)
8% to <10% (64 to <86 mmol/mol)	16,041 (19.4)	8202 (19.5)	4115 (20.8)	1910 (19.8)	899 (13.4)	915 (21.1)
≥10% (>86 mmol/mol)	7744 (9.4)	4077 (9.7)	1740 (8.8)	998 (10.4)	533 (7.9)	396 (9.1)
Unavailable	39,167 (47.4)	21,004 (49.9)	8830 (44.5)	4372 (45.4)	3172 (47.3)	1789 (41.2)

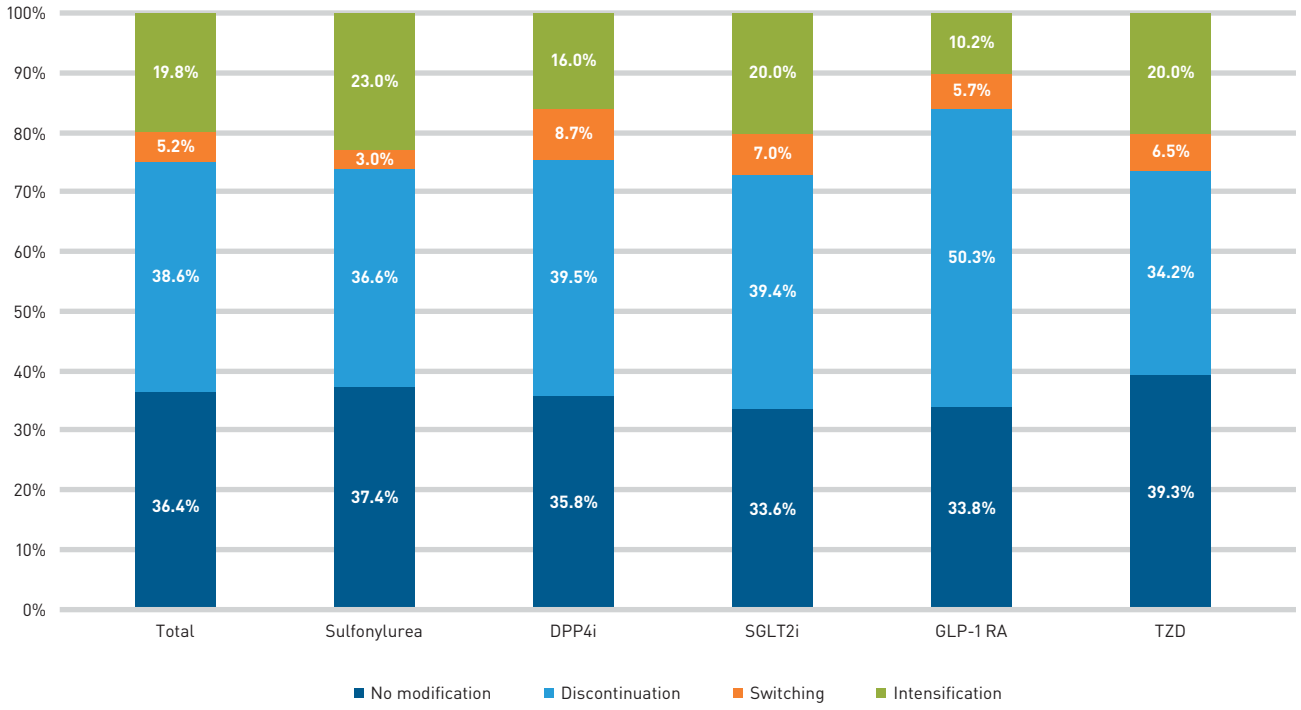
CDHP, consumer-driven health plan; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sulfonylurea, sulfonylurea/meglitinide; TZD, thiazolidinedione.

[a] Column percentage data are presented for all covariate subgroups.

the 1924 patients initially prescribed SGLT2is who intensified treatment (177; 9.2%).

In multivariable regression analysis using multivariable Cox proportional hazards models, some index medication classes had a higher adjusted risk of treatment discontinuation than sulfonylureas (**Table 3**). Compared with patients initially prescribed sulfonylureas, the adjusted risk of discontinuation was 7% higher (HR, 1.07; 95% CI, 1.04-1.10) among patients initially prescribed DPP4is and 28% higher (HR, 1.28; 95% CI, 1.23-1.33) among patients initially prescribed GLP-1 RAs. There was no adjusted difference in discontinuation between those initially prescribed sulfonylureas, SGLT2is, or TZDs.

FIGURE. Unadjusted Proportions of Treatment Modification Outcomes by Index Medication Class



DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sulfonylurea, sulfonylurea/meglitinide; TZD, thiazolidinedione.

TABLE 2. Detailed Unadjusted Results on Treatment Switching and Intensification by Index Medication Class

		Index medication class				
Treatment modification outcome	**Total**	**Sulfonylurea**	**DPP4i**	**SGLT2i**	**GLP-1 RA**	**TZD**
n	82,624	42,118	19,830	9624	6707	4345
Switching, n	4342[a]	1279[a]	1729[a]	669[a]	384[a]	281[a]
To sulfonylurea, n (%)	1429 (32.9)	N/A	978 (56.6)	220 (32.9)	117 (30.5)	114 (40.6)
To DPP4i, n (%)	1055 (24.3)	602 (47.1)	N/A	267 (39.9)	98 (25.5)	88 (31.3)
To SGLT2i, n (%)	819 (18.9)	295 (23.1)	340 (19.7)	N/A	144 (37.5)	40 (14.2)
To GLP-1 RA, n (%)	679 (15.6)	220 (17.2)	276 (16.0)	144 (21.5)	N/A	39 (13.9)
To TZD, n (%)	360 (8.3)	162 (12.7)	135 (7.8)	38 (5.7)	25 (6.5)	N/A
Intensification, n	16,327[b]	9679[b]	3171[b]	1924[b]	682[b]	871[b]
Add sulfonylurea, n (%)	1474 (9.0)	N/A	933 (29.4)	203 (10.6)	139 (20.4)	199 (22.8)
Add DPP4i, n (%)	1399 (8.6)	992 (10.2)	N/A	267 (13.9)	46 (6.7)	94 (10.8)
Add SGLT2i, n (%)	1380 (8.5)	408 (4.2)	669 (21.1)	N/A	227 (33.3)	76 (8.7)
Add GLP-1 RA, n (%)	823 (5.0)	303 (3.1)	209 (6.6)	245 (12.7)	N/A	66 (7.6)
Add TZD, n (%)	580 (3.6)	310 (3.2)	181 (5.7)	51 (2.7)	38 (5.6)	N/A
Increase index medication dose ≥ 100%, n (%)	8559 (52.4)	6602 (68.2)	643 (20.3)	981 (51.0)	N/A	333 (38.2)
Initiate basal insulin, n (%)	2112 (12.9)	1064 (11.0)	536 (16.9)	177 (9.2)	232 (34.0)	103 (11.8)

ADM, antidiabetic medication; CDHP, consumer-driven health plan; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; N/A, not applicable; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sulfonylurea, sulfonylurea/meglitinide; TZD, thiazolidinedione.

[a]Percentages reflect the percentage of patients within each column who switched to a different ADM treatment (eg, of the 4342 total patients who switched ADM treatment, 32.9% switched to a sulfonylurea).

[b]Percentages reflect the percentage of patients in each column who used individual forms of treatment intensification (eg, of the 16,327 total patients who intensified ADM treatment, 9.0% added a sulfonylurea and 52.4% doubled [or more] the dose of their index medication).

TABLE 3. Results of Multivariable Cox Proportional Hazards Models Investigating the Time to Each Treatment Modification Outcome[a]

Variable	Treatment modification outcome		
	Discontinuation, HR (95% CI)	Switching, HR (95% CI)	Intensification, HR (95% CI)
Index medication class			
Sulfonylurea (ref)	1.00	1.00	1.00
DPP4i	1.07 (1.04-1.10)	2.88 (2.68-3.10)	0.70 (0.67-0.73)
SGLT2i	1.03 (0.99-1.07)	2.25 (2.04-2.48)	0.83 (0.79-0.88)
GLP-1 RA	1.28 (1.23-1.33)	1.73 (1.54-1.95)	0.40 (0.37-0.44)
TZD	0.98 (0.92-1.03)	2.25 (1.98-2.57)	0.92 (0.86-0.99)
Age group in years			
18-44 (ref)	1.00	1.00	1.00
45-54	0.82 (0.79-0.85)	0.83 (0.75-0.92)	0.94 (0.89-0.99)
55-64	0.73 (0.70-0.75)	0.78 (0.71-0.86)	0.82 (0.78-0.87)
65-74	0.69 (0.66-0.72)	0.71 (0.62-0.80)	0.67 (0.63-0.72)
≥75	0.70 (0.66-0.74)	0.63 (0.54-0.74)	0.53 (0.49-0.58)
Sex			
Men (ref)	1.00	1.00	1.00
Women	1.13 (1.10-1.16)	1.30 (1.23-1.38)	1.09 (1.06-1.12)
Prescribing clinician			
Family medicine physician (ref)	1.00	1.00	1.00
Endocrinologist	0.91 (0.86-0.96)	1.12 (0.98-1.28)	1.36 (1.27-1.46)
Internal medicine physician	1.04 (1.01-1.06)	0.99 (0.92-1.06)	0.96 (0.92-0.99)
Nurse practitioner/physician assistant	1.11 (1.07-1.15)	1.15 (1.04-1.27)	1.02 (0.97-1.08)
Other	1.14 (1.10-1.18)	1.10 (0.99-1.21)	1.08 (1.02-1.13)
Insurance segment/CDHP			
Commercial, no CDHP (ref)	1.00	1.00	1.00
Commercial, CDHP	1.08 (1.05-1.12)	1.20 (1.10-1.32)	0.97 (0.92-1.02)
Medicare Advantage	0.87 (0.83-0.92)	1.13 (0.98-1.30)	1.12 (1.04-1.20)
Health plan structure			
Health maintenance organization (ref)	1.00	1.00	1.00
Exclusive provider organization	1.04 (0.98-1.10)	1.16 (0.99-1.36)	0.97 (0.89-1.05)
Indemnity	0.72 (0.61-0.84)	1.04 (0.69-1.58)	0.94 (0.76-1.17)
Point of service	1.01 (0.98-1.06)	1.14 (1.02-1.27)	1.05 (0.99-1.11)
Preferred provider organization	1.05 (0.99-1.12)	1.16 (0.98-1.36)	0.97 (0.90-1.06)
Other	1.01 (0.97-1.05)	1.02 (0.92-1.14)	0.91 (0.86-0.96)
DCSI score			
0 (ref)	1.00	1.00	1.00
1	1.00 (0.97-1.03)	1.09 (1.00-1.18)	1.13 (1.09-1.18)
2	1.00 (0.96-1.04)	1.23 (1.12-1.36)	1.22 (1.16-1.29)
≥3	1.02 (0.98-1.07)	1.04 (0.92-1.17)	1.32 (1.24-1.39)
Most recent HbA_{1c} level			
<8% (<64 mmol/mol) (ref)	1.00	1.00	1.00
8% to <10% (64 to <86 mmol/mol)	0.92 (0.89-0.96)	1.18 (1.07-1.29)	1.40 (1.33-1.47)
≥10% (>86 mmol/mol)	1.10 (1.06-1.15)	1.43 (1.28-1.60)	1.90 (1.79-2.01)
Unavailable	1.01 (0.98-1.04)	1.15 (1.06-1.24)	1.41 (1.35-1.47)

CDHP, consumer-driven health plan; DCSI, Diabetes Complications Severity Index; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; ref, referent category; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sulfonylurea, sulfonylurea/meglitinide; TZD, thiazolidinedione.

[a]The table presents results of multivariable Cox proportional hazards models, which evaluated differences in the time to each treatment modification outcome. In addition to including all variables listed in the table, each regression model adjusted for US Census region and the year of the index date.

Patients initially prescribed sulfonylureas had the lowest adjusted risk of switching and the highest adjusted risk of intensification. Among other index medication classes, the adjusted risk of switching ranged from being 73% greater for GLP-1 RAs (HR, 1.73; 95% CI, 1.54-1.95) to 188% greater for DPP4is (HR, 2.88; 95% CI, 2.68-3.10) compared with sulfonylureas. Conversely, the adjusted risk of intensification ranged from being 8% lower for TZDs (HR, 0.92; 95% CI, 0.86-0.99) to 60% lower for GLP-1 RAs (HR, 0.40; 95% CI, 0.37-0.44) compared with sulfonylureas. In sensitivity analyses omitting patients who switched or intensified within 1 week of the index date, inference for each index medication class was identical (results available from authors upon request).

After multivariable adjustment, several covariates were independently associated with treatment modification (Table 3). Compared with all older age groups, patients aged 18 to 44 years were at significantly higher risk of discontinuation, switching, and intensification. Men were at significantly lower risk of each modification than women. The type of prescribing clinician was associated with multiple modifications; for example, compared with having the index medication prescribed by either a family medicine physician or internal medicine physician, prescription by an endocrinologist was associated with both lower discontinuation risk and higher intensification risk. Higher DCSI scores were associated with incrementally greater intensification risk, and higher recent HbA_{1c} levels were associated with incrementally higher risks of both switching and intensification.

DISCUSSION

In this retrospective cohort study of more than 80,000 privately insured patients who initiated a second-line ADM, nearly two-thirds of included patients modified treatment within 1 year of their index medication fill. Discontinuation was by far the most common modification (38.6%), followed by intensification (19.8%) and switching (5.2%). Patients initially prescribed GLP-1 RAs had the highest observed risk of discontinuation. Patients initially prescribed sulfonylureas had the lowest adjusted risk of switching and the highest adjusted risk of

intensification (largely via increased dose of their sulfonylurea). Several variables were independently associated with treatment modifications; for example, being in a younger age group and female were both associated with higher risks of all 3 modification outcomes. Also, compared with index medication prescription by a family medicine or internal medicine physician, prescription by an endocrinologist was associated with lower discontinuation risk and higher intensification risk.

Consistent with the literature, discontinuation of second-line ADM treatment was relatively common in patients with type 2 diabetes. The particularly high discontinuation rate for GLP-1 RAs was likely due to previously observed factors such as gastrointestinal adverse effects.[26] Although our observed rates of discontinuation exceed those from a national study of outpatient electronic health record data between 1995 and 2016—in which discontinuation ranged between 10% for patients prescribed sulfonylureas and 21% for patients prescribed GLP-1 RAs and SGLT2is[12]—they are similar to those of a study of patients in managed care plans, 35% of whom discontinued ADM therapy between 2006 and 2009.[27]

The observed persistence of sulfonylurea therapy—patients with a sulfonylurea index medication rarely switched to a different ADM class or initiated a second index medication class—was notable. This finding may be indicative of elevated price sensitivity (for co-pays) among patients with a sulfonylurea index medication, who were somewhat more likely than the overall study population to be 65 years or older or to have a Medicare Advantage plan. Price sensitivity among these patients would generally align with findings from a prior study that found the high out-of-pocket costs of brand-name ADMs were associated with medication nonadherence and discontinuation in Medicare patients.[20]

From the perspective of health plan design and administration, this study's outcomes highlight the need to better understand barriers to ADM adherence in the alarmingly large number of patients who discontinued second-line therapy. When patients discontinue a second-line ADM soon after treatment initiation, both resources (among health plans and patients) and time (among patients and clinicians) are wasted. Additionally, medication nonadherence in diabetes increases the likelihood of subsequent inpatient admissions[28-30] and avoidable health care costs,[28-31] underscoring the need for interventions that promote informed prescribing practices and postprescription patient supports that maximize medication adherence after initiation of second-line ADM therapy. Research is especially needed to examine patients' reasons for discontinuation and the extent to which patients' discontinuation decisions were made without—or in conflict with—physician feedback. Research and intervention development efforts should prioritize groups shown here to be at high risk of discontinuation, including patients prescribed GLP-1 RAs, relatively younger patients, women, and patients with CDHPs.

Limitations and Strengths

This study had several limitations. Patients who switched medications within the same index medication class or gradually increased their index medication dose over time (which could eventually lead to doubling of their initial dose) were classified as having no treatment modifications. Claims data do not provide contextual information on patients' or clinicians' decision-making processes, thus precluding investigation of underlying reasons for observed treatment modifications. Also, the study did not include patients who were prescribed basal insulin as a second-line ADM.[32] Because it is often not possible to properly estimate days' supply of insulin,[33] we were unable to accurately calculate treatment modification outcomes for patients taking basal insulin. Also, prior research by our team identified distinct characteristics among patients prescribed basal insulin, including elevated HbA_{1c} and high health care costs,[13,19] compared with patients prescribed noninsulin second-line ADMs; assuming some unique characteristics of these patients remain unmeasured, including them in the current study would introduce selection bias into relevant statistical comparisons. Finally, our use of a 60-day threshold—after the prior fill was exhausted—for defining treatment modification outcomes represented a middle ground between a more stringent 30-day threshold[34] and a more permissive 90-day threshold[35] that have been used in prior medication adherence studies. A threshold of a different length would have led to different observed proportions of each treatment modification outcome.

This study also had notable strengths. To our knowledge, this was the first large study of treatment modifications for second-line ADM therapy that solely focused on the years after the 2013 introduction of SGLT2is. The large data set provided evidence on nationwide patterns of treatment modifications in privately insured populations, facilitating comprehensive comparisons across multiple classes of second-line ADM therapy. Detailed pharmacy claims data allowed for construction of valid outcome measures, with clinical and sociodemographic data leveraged to identify patient and provider characteristics that were associated with the treatment modifications under study.

CONCLUSIONS

Most included patients modified their type 2 diabetes medication regimen within 1 year of initiating a noninsulin second-line ADM, most frequently via discontinuation of their index medication. Future research is needed to improve our understanding of barriers to ADM adherence among patients who discontinue second-line therapy and to test new prescribing approaches and patient supports to maximize medication adherence and reduce health system waste among patients who initiate second-line ADM therapy. ■

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Author Affiliations: Division of General Internal Medicine (DTL, MC, MJO, CA, AJC, RTA), Institute for Public Health and Medicine (DTL, MJO, RHK, CA, AW, RTA), and Division of Endocrinology, Metabolism, and Molecular Medicine (AW, RTA), Northwestern University Feinberg School of Medicine, Chicago, IL; Applied Research, UnitedHealth Group (EK, EDP), Minneapolis, MN.

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Authorship Information: Concept and design (DTL, MJO, RHK, AW, EDP, RTA); acquisition of data (AJC, CA, EK, EDP, RTA); analysis and interpretation of data (DTL, MC, MJO, RHK, AW, AJC, EK, EDP, RTA); drafting of the manuscript (DTL, MC, EDP); critical revision of the manuscript for important intellectual content (DTL, MJO, RHK, AW, EDP, RTA); statistical analysis (DTL, MC, RHK, AJC); obtaining funding (CA); administrative, technical, or logistic support (AJC, CA, EK); and supervision (DTL).

Address Correspondence to: David T. Liss, PhD, Division of General Internal Medicine, Northwestern University Feinberg School of Medicine, 750 N Lake Shore Dr, 10th Floor, Chicago, IL 60611. Email: david.liss@northwestern.edu.

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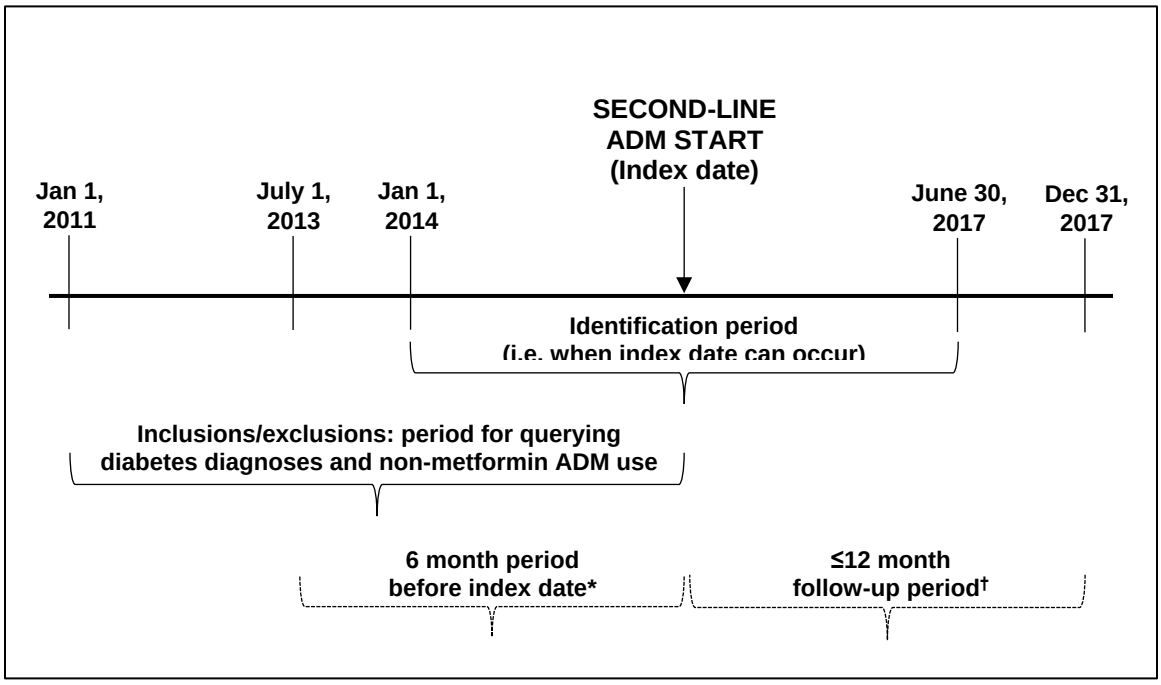
eAppendix Table. Sampling approach and inclusion/exclusion criteria applied to identify final study cohort

Inclusion/Exclusion Criteria	**Patients Excluded**	**N, Remaining Cohort**
Patients who, between 1/1/2014 and 6/30/2017, had a pharmacy claim for ≥28 day supply of 1 second-line ADM that was a sulfonylurea/meglitinide, DPP-4, GLP-1 RA, SGLT-2i, or TZD (date of claim defined as index date)	n/a	662,362
Require ≥2 outpatient diagnosis codes or ≥1 inpatient diagnosis codes for Type 2 diabetes before the index date (without accompanying diagnosis codes for Type 1 diabetes)	8,313	654,049
Require ≥1 pharmacy claim for metformin during 6 months before index date	383,359	270,690
Exclusion: prior insulin use	23,824	246,866
Exclusion: any pharmacy claims for a non-metformin ADM before the index date	128,321	118,545
Exclusion: pregnancy or childbirth during period ±6 months of index date	7	118,538
Exclusion: glucocorticoid use during 6 months before index date	2,290	116,248
Exclusion: evidence of a rare condition (e.g. acromegaly, hemochromatosis, sulfa allergy, Cushing syndrome, cystic fibrosis, medullary thyroid) before index date	1,492	114,756
Exclusion: age <18	25	114,731
Exclusion: missing data for any variables used in regression analysis	8	114,723
Exclusion: not continuously enrolled in a commercial or Medicare Advantage health plan, with no change in health plan insurance segment, during period ±6 months of index date	32,099	82,624
Final study cohort		**82,624**

Abbreviations: ADM, anti-diabetes medication; DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione;

eAppendix Figure. Dates of data collection and identification of study periods for included patients



Abbreviations: ADM, anti-diabetes medication

*Continuous health plan enrollment required during this 6-month period

† Continuous health plan enrollment required for first ≤6 months of this period