Risk factors associated with treatment discontinuation and down-titration in type 2 diabetes patients treated with sulfonylureas

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ABSTRACT

Objectives: Sulfonylurea therapy among patients with type 2 diabetes mellitus (T2DM) can be disrupted due to adverse events, including hypoglycemia. A retrospective study using the MarketScan claims database quantified the frequency of sulfonylurea discontinuation or down-titration and identified associated risk factors.

Research design and methods: Adult patients with an index sulfonylurea prescription between 2008 and 2012 and 1 year continuous enrollment pre- and post-index were included. Therapy changes assessed over 1 year post-index included discontinuation and down-titration. Discontinuation occurred if the date of a fill was >90 days from the end date of the preceding fill. Down-titration occurred when a fill had a lower equivalent dose than the fill on the index date. Kaplan–Meier methods estimated the probability of either discontinuation or down-titration over 12 months, and Cox regression models identified associated risk factors.

Results: A total of 104,082 sulfonylurea users were included in the study and the probability of either discontinuation or down-titration at 3, 6, and 12 months was 23.2%, 38.9%, and 52.3%, respectively. Major risk factors associated with therapy changes included post-index hypoglycemia (discontinuation hazard ratio [HR] = 1.78 [1.68, 1.89]; down-titration HR = 2.79 [2.40, 3.23]) and concomitant use of insulin (discontinuation HR = 1.48 [1.40, 1.57]; down-titration HR = 1.82 [1.56, 2.11]). Other risk factors included younger age, female gender, use of second generation sulfonylureas, prior cardiovascular comorbidity and liver disease.

Limitations: The study was not able to assess unreported, potentially mild cases of hypoglycemia, nor was it able to evaluate the association between changes in therapy and HbA1c levels or body weight.

Conclusions: More than half of T2DM patients who initiated sulfonylurea therapy discontinued or down-titrated within 1 year. Insulin use and hypoglycemia were associated with sulfonylurea therapy change.

Introduction

The prevalence of diabetes in the US is estimated at 9.3% and is associated with significant mortality and morbidity. Adults with diabetes have 1.5 times the risk of death compared with those without the condition after adjusting for age. Diabetes also presents a significant economic burden, costing the US economy $245 billion in direct medical costs and another $69 billion in indirect costs in 2012. Complications due to diabetes are responsible for a significant portion of these costs. The effective management of diabetes reduces the risk of complications, and thus the individual and societal burden of the disease.

Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diabetes in the US. Several oral antihyperglycemic agents (OAHAs) have been developed to improve glycemic control in patients with T2DM and reduce the risk of complications. After metformin, sulfonylureas are the second most common class of OAHAs because they have proven efficacy and are low in cost. However, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) cite that sulfonylureas lack glycemic durability and are associated with modest weight gain and hypoglycemia. The ADA states that sulfonylureas should be substituted with other classes of OAHAs in the event of troublesome hypoglycemia. The AACE further cautions that hypoglycemia may be more prolonged when longer-acting formulations are used in the elderly, and that renal insufficiency increases the risk of sulfonylurea-associated hypoglycemia. Overall, clinical guidelines stress the importance of a patient-centered approach to diabetes management that considers each patient individually, including their demographics, health history and preferences.

Therapy persistence is an important component of effective diabetes management. However, discontinuation is a challenge across all classes of OAHAs, with an estimated 12 month persistence of 62%. Given the increased risk of hypoglycemia and weight gain, sulfonylurea therapy may be...
discontinued or down-titrated more often than other OAHAs, and observational studies have found that the 12 month persistence of therapy with sulfonylureas is significantly lower compared with other OAHAs13–15. A retrospective study in the US found that persistence with sulfonylurea therapy was 56% at 12 months and fell to 46% after 24 months15. Similar findings have been documented outside of the US, and a study of patients with T2DM in general practice in Germany found that 49% of patients had discontinued sulfonylurea therapy within 2 years of initiation16. Results were also consistent in a recent prospective study, where combination therapy with sulfonylureas was found to have shorter treatment duration and higher occurrence of hypoglycemia compared with other combination therapies17.

While previous studies have explored the persistence of sulfonylurea therapy among T2DM patients, there remains a lack of understanding regarding the rate of both discontinuation and down-titration in real-world clinical practice in the US, as well as their associated risk factors. To address this gap, the objectives of this study are (1) to describe discontinuation and down-titration within 1 year of sulfonylurea initiation for the treatment of T2DM; and (2) to assess and quantify the association between therapy discontinuation and down-titration with relevant characteristics.

Patients and methods

**Study design and data**

A retrospective cohort study of patients with T2DM assessed discontinuation and down-titration within 1 year of initiating sulfonylurea therapy between 2008 and 2012. The study utilized the MarketScan Commercial Claims and Encounter Database and the Medicare Supplemental Database. The Commercial Claims database is composed of healthcare claims from individuals less than 65 years of age who have employer-sponsored private health insurance, including their dependents. The database includes more than 100 healthcare plans in the US across all census regions, including comprehensive plans, exclusive provider organizations, preferred provider organizations, point-of-service plans (with and without capitation), and health maintenance organizations. The Medicare Supplemental Database contains patients 65 years or more, and their spouses, who are enrolled in Medicare with supplemental Medigap insurance paid by their former employers. In 2013, all Marketscan databases captured full information on inpatient, outpatient and pharmacy claims for approximately 66 million individuals18.

Patients were considered in this analysis if they had at least one pharmacy claim for a sulfonylurea between 1 January 2008 and 31 December 2012 (study period). Sulfonylureas under consideration included first generation sulfonylureas (i.e. chlorpropamide; tolazamide; tolbutamide), second generation sulfonylureas (i.e. glipizide; glyburide) and third generation sulfonylureas (i.e. glimepiride). The date of the first pharmacy claim for a sulfonylurea within the study period was defined as the index date, and the sulfonylurea filled on that index date was referred to as the index drug. Patients were included in the analysis if they were aged 18 years or older as of the index date and had continuous enrollment 1 year pre- and post-index. Patients were excluded if they had a diagnosis of type 1 diabetes during the study period; had a diagnosis of gestational or secondary diabetes 1 year pre- and post-index; were treated with insulin 1 year pre-index; had incomplete dosing or days of supply for sulfonylureas 1 year post-index; or had pharmacy claims for two or more types of sulfonylurea on the index date.

**Outcomes and measures**

The main outcomes of the study were type of therapy change and time to therapy change 1 year post-index. All patients were classified into the following mutually exclusive comparison groups, based on the first of any therapy change within 1 year post-index: discontinuers, down-titraters or continuers. Therapy discontinuation occurred if the date of a subsequent prescription fill for a sulfonylurea was more than 90 days apart (the permissible gap) from the end date of the preceding fill, and the end date of the preceding fill was referred to as discontinuation date. Therapy down-titration occurred if the daily dose of a subsequent fill was lower than the index dose, and the down-titration date was defined as the date of the first subsequent fill with the lower dose. If no therapy change occurred, patients were classified as continuers.

Pre-index measures assessed included patient demographics, region, health plan type, and pre-index diabetes-related comorbidities, including microvascular complications, macrovascular complications, chronic kidney disease, liver disease and pre-index hypoglycemia. Comorbidities of interest and hypoglycemia were determined using ICD-9-CM codes associated with each claim (see Supplementary Table 1 for ICD-9-CM codes used). Post-index measures included generation of index sulfonylurea, index dose, type of combination therapy, and index year. Doses for different sulfonylurea drugs were converted to the equivalent dose of glyburide following the cited conversion table in order to allow patients to switch between sulfonylurea drugs19. For example, 1 mg of glimepiride was considered equivalent to 2.5 mg of glyburide. Combination therapy was defined as the presence of fills for another non-sulfonylurea agent within 60 days before or 30 days after the index date, and included metformin, thiazolidinediones, meglitinides, glucagon-like peptide-1 agonists (GLP-1), dipeptidyl peptidase-4 inhibitors (DPP-4), α-glucosidase inhibitors, insulin or another antidiabetic agent. Post-index hypoglycemia and diabetes-related comorbidities were also assessed over 1 year or up to the time of therapy change, whichever occurred first.

**Statistical analysis**

Descriptive analyses summarized pre- and post-index measures overall and by type of therapy change. Between-group differences were assessed using chi-squared tests and Kruskal–Wallis tests for categorical and continuous variables, respectively. Average time to discontinuation was calculated as the number of days between the index and
discontinuation dates among discontinuers only. Average
time to down-titration was calculated as the number of days
between the index and down-titration dates among down-
titraters only. Time to either discontinuation or down-titration
was estimated for the entire sample utilizing the
Kaplan–Meier (KM) method, and the probability of either
discontinuation or down-titration was assessed at 3, 6 and
12 months.

Multivariate Cox hazard regression analysis was then used
to analyze risk factors associated with time to either discon-
tinuation or down-titration. Hazard ratios (HRs) quantified
the association between therapy change and each variable
of interest. Patient demographics, health plan type, index
sulfonylurea generation, type of combination therapy and
pre-index diabetes-related comorbidities were included as
time-independent predictors (for a full list of variables
included in the model, please refer to Table 3). Post-index
hypoglycemia was included as a time-varying predictor. Two
sub-event analyses were also conducted to assess the associ-
ation between post-index hypoglycemia and discontinuation
and down-titration separately, using two separate multivariate
models. For the analysis of discontinuation, down-titraters
were excluded from the regression model. For the analysis of
down-titration, discontinuers were excluded from the model.
Wald's statistics were used to evaluate 95% confidence inter-
vals (CIs) and p-values. A p-value of less than 5% was consid-
ered statistically significant throughout the analysis.

A sensitivity analysis was conducted in a subgroup of
patients who did not use or switch to insulin therapy within
the 1 year post-index. This analysis was completed in order to
explore risk factors associated with therapy change that was
not driven by a need for greater glycemic efficacy, such as
the addition of insulin, but instead potentially caused by
other factors, including adverse events. This sensitivity ana-
lysis also explored results after removing any potential excess
risk of hypoglycemia among patients with insulin use.

Results

Sample selection and characteristics

Figure 1 outlines the sample selection. A total of 708,796
patients were initially identified as having at least one pre-
scription for a sulfonylurea between 1 January 2008 and 31
December 2012. Of these 136,722 patients were both 18
years or older and had 1 year continuous enrollment pre- and
post-index. After applying all exclusion criteria, the final sam-
pole comprised 104,082 patients. Table 1 summarizes pre-index
patient characteristics as a whole and by each type of therapy
change. Overall, 49,158 patients (47.2%) were discontinuers,
6075 (5.8%) were down-titraters and 48,849 (46.9%) continued
sulfonylurea therapy without down-titration; 56.2% of the
total sample was male, and the average patient age was 57.0
years. Discontinuers and down-titraters were significantly
younger compared with continuers \(p < 0.01\). A significantly
smaller proportion of patients who continued therapy in the
post-index period had a history of hypoglycemia compared
with those who discontinued or down-titrated sulfonylurea
therapy \(p < 0.01\). Similarly, a smaller proportion of patients

Descriptive analysis

Table 2 presents post-index measures, including the gener-
ation of index drug, index dose and combination therapy. Overall, 64.7% of patients initiated a second generation sulfo-
ylurea, 35.3% initiated a third generation sulfonylurea and
only 0.1% of patients initiated a first-generation sulfonylurea.
The average equivalent dose upon initiation was 6.2 mg for
all patients, and down-titraters had a higher index dose com-
pared with the other subgroups (8.7 mg for down-titraters vs.
6.2 mg for discontinuers vs. 5.8 mg for continuers; \(p < 0.01\);
70.7% of all patients received combination therapy upon sul-
fonylurea therapy initiation. Metformin (63.7%), thiazolidine-
diones (11.6%) and DPP-4 inhibitors (10.2%) were most
commonly combined with sulfonylurea therapy, while 2.1% of
patients used insulin. In the 1 year post-index period, 2.7% of
patients experienced hypoglycemia, which was measured
before any therapy change. A higher proportion of patients
who down-titrated their sulfonylurea therapy experienced
post-index hypoglycemia compared with those who discon-
tinued or continued without down-titration (3.5% for
Table 1. Pre-index patient characteristics.

| Region                  | Overall $N$ | %   | Discontinuers $N$ | %   | Down-titraters $N$ | %   | Continuers $N$ | %   | p-value |
|-------------------------|-------------|-----|-------------------|-----|-------------------|-----|----------------|-----|---------|
| Male                    | 58,543      | 56.2| 26,648            | 54.2| 3467              | 57.1| 28,428         | 58.2| <0.01   |
| North central           | 29,425      | 28.3| 13,059            | 26.6| 1766              | 29.1| 14,600         | 29.9| <0.01   |
| South                   | 44,176      | 42.4| 22,291            | 45.3| 2623              | 43.2| 19,262         | 39.4| <0.01   |
| West                    | 17,800      | 17.1| 8505              | 17.3| 977               | 16.1| 8318           | 17.0|         |
| Unknown                 | 3309        | 3.2 | 1055              | 2.1 | 192               | 3.2 | 2062           | 4.2 |         |
| Health maintenance organization (HMO) | 17,240 | 16.6 | 8485 | 17.3 | 906 | 14.9 | 7849 | 16.1 | <0.01 |
| Point of service (POS)  | 8268        | 7.9 | 3966              | 8.1 | 468               | 7.7 | 3834           | 7.8 |         |
| Preferred provider organization (PPO) | 55,373 | 53.2 | 26,242 | 53.4 | 3320 | 54.7 | 25,811 | 52.8 |         |
| Other                   | 23,201      | 22.3| 10,465            | 21.3| 1381              | 22.7| 11,355         | 23.2|         |

Pre-index diabetes-related comorbidities

| Microvascular complications | Overall $N$ | %   | Discontinuers $N$ | %   | Down-titraters $N$ | %   | Continuers $N$ | %   | p-value |
|-----------------------------|-------------|-----|-------------------|-----|-------------------|-----|----------------|-----|---------|
| Retinopathy                 | 4564        | 4.4 | 1925              | 3.9 | 294               | 4.8 | 2345           | 4.8 | <0.01   |
| Neuropathy                  | 7059        | 6.8 | 3326              | 6.8 | 467               | 7.7 | 3266           | 6.7 | 0.01    |
| Nephropathy                 | 5092        | 4.9 | 2253              | 4.6 | 370               | 6.1 | 2469           | 5.1 | <0.01   |

Macrophascular complications

| Stroke                      | 1539        | 1.5 | 724               | 1.5 | 134               | 2.2 | 681            | 1.4 | <0.01   |
| Transient ischemic attack   | 1227        | 1.2 | 572               | 1.2 | 100               | 1.6 | 555            | 1.1 | <0.01   |
| Congestive heart failure    | 4469        | 4.3 | 2086              | 4.3 | 313               | 5.2 | 2070           | 4.2 | <0.01   |
| Myocardial infarction       | 2164        | 2.1 | 1060              | 2.2 | 161               | 2.7 | 943            | 1.9 | <0.01   |
| Ischemic heart diseases     | 13,483      | 13.0| 6104              | 12.4| 834               | 13.7| 6545           | 13.4| <0.01   |
| Peripheral arterial diseases| 4552        | 4.4 | 2136              | 4.3 | 319               | 5.3 | 2097           | 4.3 | <0.01   |
| Chronic kidney diseases     | 5344        | 5.1 | 2546              | 5.2 | 352               | 5.8 | 2446           | 5.0 | 0.03    |
| Liver diseases              | 3104        | 3.0 | 1617              | 3.3 | 182               | 3.0 | 1305           | 2.7 | <0.01   |
| Hypoglycemia                | 2515        | 2.4 | 1284              | 2.6 | 167               | 2.7 | 1064           | 2.2 | <0.01   |

*p-values were calculated using chi-square tests for categorical variables and Kruskal–Wallis nonparametric ANOVA for continuous variables.

down-titraters vs. 2.4% for discontinuers vs. 2.8% for continuers; $p < 0.01$). Compared with continuers, a significantly greater percentage of patients who down-titrated or discontinued sulfonylurea therapy experienced post-index diabetes-related comorbidities, including stroke, TIA, congestive heart failure and MI ($p < 0.01$ for all).

Overall, 53.1% of patients experienced either sulfonylurea discontinuation or down-titration within 1 year post-index, with an average time to first therapy change of 124.2 days (median = 91 days). The average time to discontinuation among discontinuers was 122.7 days (median = 91 days) and the average time to down-titration among down-titraters was 137.0 days (median = 114 days). Figure 2 presents KM curves, and demonstrates that at 3, 6 and 12 months, the probability of second generation sulfonylurea versus third generation sulfonylureas was 9% more likely to use sulfonylurea therapy experienced post-index diabetes-related comorbidities, including stroke, TIA, congestive heart failure and MI ($p < 0.01$ for all).

**Multivariable regression analysis**

Table 3 presents results from multivariable Cox hazard regression models for the time to therapy change (either discontinuation or down-titration), as well as two sub-event analyses for time to discontinuation and time to down-titration separately. The results demonstrate that time to therapy change was significantly associated with post-index hypoglycemia after adjusting for patient characteristics, comorbidities and combination therapy. Patients with post-index hypoglycemia were approximately 82% more likely to have any change in sulfonylurea therapy within 1 year compared with patients who did not experience post-index hypoglycemia (HR = 1.82; 95% CI = [1.72, 1.93]). Sub-event analyses suggested that post-index hypoglycemia had a larger effect on the rate of down-titration than discontinuation. It was associated with a 179% increase in the rate of down-titration (HR = 2.79; 95% CI = [2.40, 3.23]) and a 78% increase in the rate of discontinuation (HR = 1.78; 95% CI = [1.68, 1.89]).

Regression analyses also identified other independent risk factors associated with sulfonylurea therapy discontinuation or down-titration beyond hypoglycemia, and demonstrated that therapy change was significantly, separately and positively associated with being female, younger age, and the use of second generation sulfonylureas versus third generation (p < 0.01). There were also significant differences in the rate of therapy change across types of combination therapy. For example, patients combining insulin with sulfonylureas were 48% more likely to experience any change in sulfonylurea therapy compared with their counterparts (HR = 1.48; 95% CI = [1.40, 1.56]). There was also a significantly increased rate of treatment change associated with a history of neuropathy, stroke, MI and peripheral arterial disease (PAD). Patients with chronic kidney disease were 7% more likely to change therapy compared to patients without kidney disease (HR = 1.07; 95% CI = [1.03, 1.11]) and patients with liver diseases were 9% more likely to change therapy compared to their counterparts (HR = 1.09; 95% CI = [1.04, 1.14]).

Sensitivity analysis among a subgroup of patients who did not receive insulin therapy within 1 year post-index ($n = 97,570$) found that 52.1% of these patients experienced...
discontinuation or down-titration within 1 year. Multivariable Cox regression analysis demonstrated that, in this subgroup, patients with post-index hypoglycemia were 86% more likely to experience any change in sulfonylurea therapy compared with patients who did not experience hypoglycemia (HR = 1.86; 95% CI = [1.75, 1.97]; results not shown).

**Discussion**

The purpose of this retrospective study was to describe real-life therapy changes and their associated risk factors among patients with T2DM who initiated therapy with sulfonylureas. Results demonstrated that more than half of T2DM patients...
they suggest that an increased rate of hypoglycemia after sulfonylurea treatment may lead to an elevated hazard of both treatment discontinuation and down-titration, and potentially challenge the effective management of diabetes.

Results from this analysis also contribute to knowledge describing risk factors for sulfonylurea therapy change beyond hypoglycemia. Patients who combined sulfonylurea therapy with insulin were significantly more likely to discontinue or down-titrator therapy after 1 year compared with patients who initiated other combination therapy. The use of second generation sulfonylureas also increased the rate of discontinuation and down-titration more than third generation sulfonylureas. Further, there was a significant association between history of some diabetes-related comorbidities and their impact on the likelihood of changing therapy, highlighting the importance of considering these factors in the management of diabetes.

### Table 3. Cox multivariable regression – Time to first therapy change.

| Variables | Time to therapy change | Time to discontinuation | Time to down-titration |
|-----------|------------------------|-------------------------|------------------------|
|           | HRb | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Post-index hypoglycemiaa | 1.82 (1.72, 1.93) | <0.01 | 1.78 (1.68, 1.89) | <0.01 | 2.79 (2.40, 3.23) | <0.01 |
| Male | 0.91 (0.89, 0.92) | <0.01 | 0.90 (0.88, 0.91) | <0.01 | 0.95 (0.90, 1.00) | 0.05 |
| Index age group | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| 26–35 vs. 18–25 | 0.79 (0.70, 0.89) | 0.77 (0.68, 0.88) | 0.78 (0.49, 1.32) |
| 36–45 vs. 18–25 | 0.62 (0.55, 0.70) | 0.61 (0.54, 0.69) | 0.60 (0.38, 1.00) |
| 46–55 vs. 18–25 | 0.49 (0.44, 0.56) | 0.47 (0.42, 0.54) | 0.51 (0.33, 0.86) |
| 56–65 vs. 18–25 | 0.43 (0.38, 0.48) | 0.40 (0.36, 0.46) | 0.45 (0.29, 0.76) |
| 66–75 vs. 18–25 | 0.41 (0.36, 0.46) | 0.38 (0.34, 0.43) | 0.48 (0.30, 0.80) |
| 75 or older vs. 18–25 | 0.40 (0.36, 0.46) | 0.37 (0.33, 0.42) | 0.54 (0.34, 0.91) |
| Residential location | <0.01 | <0.01 | <0.01 | <0.01 |
| North central vs. West | 0.96 (0.937, 0.990) | 0.95 (0.92, 0.98) | 1.06 (0.98, 1.16) |
| Northeast vs. West | 0.98 (0.945, 1.016) | 0.98 (0.94, 1.02) | 0.99 (0.89, 1.11) |
| South vs. West | 1.10 (1.076, 1.132) | 1.10 (1.07, 1.13) | 1.19 (1.10, 1.28) |
| Unknown vs. West | 0.60 (0.57, 0.65) | 0.79 (0.67, 0.93) |

- The 95% confidence intervals and p-values were evaluated using Wald’s statistics.
- A hazard ratio (HR) < 1 indicates a reduced likelihood of experiencing a therapy change.
- Post-index hypoglycemia was measured prior to any therapy change.
- The time to discontinuation model excluded patients who down-titrated therapy, while the time to down-titration model excluded patients who discontinued.

who newly initiated sulfonylurea therapy discontinued or down-titrated their therapy within 1 year. The large proportion of patients who experienced a therapy change discontinued their treatment (47% of all patients), while a smaller proportion of patients down-titrated their dose (6% of all patients). Multivariable regression analysis demonstrated that after adjusting for patient characteristics, type of combination therapy and comorbid conditions, post-index hypoglycemia was a major driver of both discontinuation and down-titration. Post-index hypoglycemia increased the rate of down-titration more than the rate of discontinuation. This suggests that after a hypoglycemic event, practitioners may first propose down-titrating sulfonylurea therapy before discontinuing treatment. Results from this analysis are important because...
therapy changes, including macrovascular complications (such as stroke, MI and PAD), chronic kidney disease and liver disease. Results were consistent with other literature that found that younger age, female gender, and greater comorbidity were associated with sulfonylurea therapy discontinuation. Overall, these findings highlight the complex reasons for lack of treatment persistence among patients with T2DM, and the importance of considering a patient's demographics, history and risk of hypoglycemia, and comorbidities when deciding the most appropriate diabetes therapy.

After 12 months of treatment, approximately 53% of patients in this study changed sulfonylurea therapy (this combines the down-titration and discontinuation groups), a measure that is comparable to previously reported 12 month sulfonylurea persistence rates between 56% and 67%.

Differences across studies may be explained by a range in the permissible gap used to define discontinuation, as well as differences in study populations. The current study used more recent data compared to previous work, and lower persistence in this analysis may reflect changing treatment patterns and acceptability of sulfonylureas over time, although we did not observe a time trend in this analysis (data not shown). Meanwhile, the result that 6% of patients down-titrated sulfonylurea therapy was similar to a study employing US pharmacy claims that reported that 11% of patients decreased their sulfonylurea dose within 12 months.

Results from this study were robust to several sensitivity analyses. First, the relationship between post-index hypoglycemia and therapy change was unaffected after removing a subgroup of patients who initiated insulin therapy (2.1% of the sample). This demonstrates that when we disregard treatment changes that are potentially related to a need for greater glycemic efficacy, such as the addition of insulin, and instead focus on changes due to safety and tolerability, hypoglycemia remains a major driver of sulfonylurea discontinuation and down-titration. It is generally advised that treatment with sulfonylureas be stopped after the initiation of insulin due to an increased risk of hypoglycemia. However, sensitivity analysis also demonstrated that the positive relationship between hypoglycemia and sulfonylurea therapy change remained consistent in the subgroup of patients without insulin use.

Another sensitivity analysis explored the effect of the permissible gap on results. This study set the permissible gap at 90 days, as suggested by previous literature. This is also supported by clinical evidence, as it is recommended that patients visit their physician every 3 months. To verify that a gap size of 90 days was appropriate for this data set, we varied the permissible gap between 45 and 180 days. The sensitivity analysis demonstrated that the size of subgroups did not vary greatly, and that overall results were not sensitive to permissible gap size (data not shown).

This study reported a lower rate of both pre- and post-index hypoglycemia (2.4% and 2.7%, respectively), compared with a meta-analysis of randomized control trials that estimated the proportion of patients with at least one hypoglycemic event at 17%. The lower rate reported in this study may be caused by measurement bias in the Marketscan database. In this study, hypoglycemia was defined when a claim had an associated ICD-9 code (250.8 – diabetes with other specified manifestations, 251.0 – hypoglycemia coma, 251.1 – other specified hypoglycemia, 251.2 – hypoglycemia, unspecified, 962.3 – poisoning by insulins and antidiabetic agents), but it was not possible to confirm the severity of hypoglycemia. Hypoglycemic events experienced by patients who did not seek treatment are not captured by Marketscan claims data. Therefore, mild to moderate hypoglycemic events are likely to be missed in this analysis, leading to an underestimation of the overall prevalence of hypoglycemia, as well as its association with treatment changes. This highlights that a large number of hypoglycemic events may escape physician knowledge and, when not treated, may hinder diabetes management.

Another unexpected result was that the proportion of patients with post-index hypoglycemia was slightly higher among continuers (2.8%) versus discontinuers (2.4%). This finding may be due to differences in the length of follow up time used to assess hypoglycemia. When a patient discontinued therapy, post-index hypoglycemia was no longer assessed, resulting in a shortened follow up period among discontinuers (average time to therapy change among discontinuers was 122.7 days) compared with continuers, who had the entire 12 month period to assess hypoglycemia.

This study faced several limitations inherent to observational studies that employ claims databases. First, the study used pharmacy and medical claims to infer patients' real-life treatment patterns and medical histories, and the accuracy of the claims cannot be fully ascertained. Second, time to therapy change was likely overestimated, as patients may change their sulfonylurea therapy before the fill pattern actually reflects this change. Also, given data limitations, regression analysis did not control for the type of doctor, history of hospitalization or a history of mental health disorders, which were found to be significantly associated with therapy change in previous research. Similarly, given limited clinical data, the study was also not able to assess the association between changes in therapy and HbA1c levels, a measure of glycemic control, or with body weight, an important adverse event. This may have led to residual confounding, and potentially explains some of the difference in the rate of therapy changes between patients with hypoglycemia and those without. Gene polymorphisms in the CYP2C9 gene have been found to be associated with an increased risk of hypoglycemia among T2DM patients treated with sulfonylureas, which may lead to discontinuation or down-titration of sulfonylurea therapy.

Unfortunately, the present study was also unable to account for inter-individual variation in CYP2C9 status. Notably, the generation of sulfonylurea was a significant risk factor for therapy change, but it should be mentioned that second generation sulfonylureas are more heterogeneous as a class than third generation. This analysis also assumed that the conversion factor for sulfonylurea dose was robust across the dose range. Also, while first generation sulfonylureas are currently not widely used, they were retained in the sample to fully capture real-world sulfonylurea use. Finally, results may not be generalizable to patients without health insurance or outside of the US. To build upon these findings,
future research could assess patient treatment patterns after sulfonylurea therapy change, and could also examine the effect of sulfonylurea therapy change on glycemic outcomes and economic costs.

Conclusion

Results from this study demonstrate that, in real life, half of patients with T2DM on sulfonylureas discontinue or down-titrated therapy within 1 year of initiation, and that post-index hypoglycemia is a major risk factor for sulfonylurea therapy change. Other important factors associated with sulfonylurea therapy change included the use of insulin therapy, younger age and a history of macrovascular complications, chronic kidney disease and liver disease. To ensure consistent and effective diabetes management, and thus reduce the burden of diabetes, providers should take a patient-centered approach that considers both the effectiveness and tolerability of sulfonylureas, along with other antihyperglycemic agents, when selecting the most appropriate treatment for T2DM.

Transparency

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Declaration of financial/other relationships

K.I. has disclosed that she is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA. P.L. has disclosed that he is an employee of MSD Portugal, Paço de Arcos, Portugal. Y.Q. has disclosed that she was employed by Merck & Co. Inc. at the time of the study, and is now an employee of Novartis Pharmaceutical Company. J.T. and Z.L. have disclosed that they are employees of Asclepius Analytics Ltd., which received fees for consulting from Merck & Co. Inc., Kenilworth, NJ, USA. C.-P.S.F. has disclosed that he was employed by Asclepius Analytics Ltd. at the time of the study, and is now an employee of the Hospital for Sick Children, Toronto, ON, Canada. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Previous presentations

Iglay K, Qiu Y, Fan C-PS, et al. Risk factors associated with treatment discontinuation and down-titrating in type 2 diabetes patients treated with sulfonylureas. 50th EASD Annual Meeting, 15–19 September 2014, Vienna, Austria. Iglay K, Qiu Y, Fan C-PS, et al. Risk factors associated with treatment discontinuation and down-titrating in type 2 diabetes patients treated with sulfonylureas. ADA 74th Scientific Sessions, 13–17 June 2014, San Francisco, CA, USA. Laires P, Iglay K, Fan C-PS, et al. Impact of hypoglycemia on discontinuing or down-titrating sulfonylurea among type 2 diabetes patients without insulin use. ISPOR 17th Annual European Congress, 8–12 November 2014, Amsterdam, The Netherlands.

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