Type 2 diabetes mellitus (T2DM) affects approximately 30.3 million individuals in the United States, a number that is expected to grow to almost 36 million by the year 2030.1,2 Diabetes is responsible for $176 billion in annual direct medical costs and for $69 billion annually in disability, lost work productivity, and premature mortality in the United States.3 The goals of diabetes treatment are to achieve glycemic control and to reduce the risk for long-term complications.4 To be able to achieve and maintain their glycemic control goals, and to avoid complications, patients should remain adherent to their prescribed treatment regimen.5

Treatments are currently available from 14 classes of antidiabetes medications, including, but not limited to, biguanides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 agonists, sodium-glucose cotransporter (SGLT)-

ORGANIZATION Archival Reprint

ORIGINAL RESEARCH

The Effects of a Sitagliptin Formulary Restriction Program on Diabetes Medication Use

Yuexin Tang, PhD; Xingyue Huang, PhD; Jinan Liu, PhD; R. Ravi Shankar MD; Michael L. Ganz, PhD; Swapnil Rajpathak, MD, DrPH

BACKGROUND: Health plans have responded to the many treatment options for type 2 diabetes mellitus by implementing formulary restriction policies, including step therapy, to control costs. Little is known about the impact of step therapy programs on antidiabetes medication use.

OBJECTIVE: To assess the impact of a sitagliptin step therapy program on antidiabetes medication use among sitagliptin users.

METHODS: Using pharmacy claims from the Symphony Health Solutions’ Integrated Dataverse, we compared the use of sitagliptin and other antidiabetes medications by patients enrolled in a health plan (Plan A) that implemented a sitagliptin step therapy program on July 1, 2013, with the use by patients who were contemporaneously enrolled in 2 comparison plans—Plans B and C—without step therapy programs. Sitagliptin—a dipeptidyl peptidase (DPP)-4 inhibitor—was in tier 3 in Plans A and B and in tier 2 in Plan C during the study period. We assessed the use of antidiabetes medications during the pre–step therapy period (January-June 2013) and the post–step therapy period (October 2013-March 2014).

RESULTS: We identified 2995 patients enrolled in Plan A, 751 enrolled in Plan B, and 394 enrolled in Plan C who received sitagliptin during the pre–step therapy period. Patient characteristics and pre–step therapy sitagliptin use were similar across plans. During the post–step therapy period, more patients in Plan A (approximately 70%) discontinued sitagliptin than patients in Plan B (approximately 51%) and Plan C (approximately 25%). Approximately 30% of patients in Plan A switched to another DPP-4 inhibitor compared with approximately 15% and 2% of patients in Plans B and C, respectively. Seventeen percent of patients in Plan A discontinued sitagliptin without replacement but continued using other antidiabetes medications compared with approximately 13% and 8% of patients in Plans B and C, respectively. In all, 17% of patients in Plans A and B and 11% of patients in Plan C discontinued using all antidiabetes medications.

CONCLUSION: The step therapy program changed patients’ use of sitagliptin, which was the target of the step therapy program, as well as of other antidiabetes medications. Most patients stopped sitagliptin treatment after the step therapy program started. Some patients discontinued sitagliptin treatment without replacement, but others discontinued using all antidiabetes medications.

KEY WORDS: diabetes mellitus, dipeptidyl peptidase-4 inhibitors, drug utilization, formulary restriction program, managed care programs, multitier formulary, sitagliptin, step therapy

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Effects of a Sitagliptin Formulary Restriction Program

KEY POINTS

- Health plans are using multitier formularies and step therapy programs to control the cost of treating type 2 diabetes.
- This study used pharmacy claims to assess the impact of a step therapy program on antidiabetes medication use among patients receiving sitagliptin.
- Patients enrolled in a health plan that implemented a sitagliptin step therapy program (Plan A) were compared with patients in plans without such a program (Plans B and C).
- The step therapy program was associated with less sitagliptin use and higher preferred drugs use.
- In the post–step therapy period, 70% of patients in Plan A discontinued sitagliptin versus 51% in Plan B and 25% in Plan C.
- In all, 30% of Plan A patients switched to another DPP-4 inhibitor compared with 15% and 2% of patients in Plans B and C, respectively.
- In Plan A, 17% of patients stopped sitagliptin treatment and continued using previous antidiabetes medications compared with 13% and 8% of patients in Plans B and C, respectively.

In a previous article, Huang and colleagues assessed the impact on medication use of a formulary restriction that moved sitagliptin—a DPP-4 inhibitor that is indicated by the US Food and Drug Administration for the treatment of T2DM—from the second to the third tier. They found that approximately 36% of patients discontinued sitagliptin after the restriction was implemented. Among those who discontinued sitagliptin therapy, approximately 44% switched to a preferred DPP-4 inhibitor. Patients who discontinued sitagliptin were more likely to switch to a GLP-1 agonist or to insulin after the sitagliptin tier change than those who continued using sitagliptin.

Despite the relatively large body of literature showing that such formulary restrictions are associated with decreased medication utilization overall, reduced adherence, and unfavorable clinical outcomes, very little is known about the effects of step therapy programs, specifically for antidiabetes medications. Our study contributes to this literature, and addresses the dearth of studies focusing on antidiabetes medications by assessing the effects of a sitagliptin step therapy program that required a trial of a preferred DPP-4 inhibitor (ie, linagliptin or saxagliptin) before sitagliptin claims would be reimbursed. Specifically, patients who had not previously received DPP-4 inhibitor therapy were required to use a preferred DPP-4 inhibitor, and current users of sitagliptin were required to switch to one of the preferred DPP-4 inhibitors.

Methods

Study Design and Sample

This descriptive, retrospective cohort study used pharmacy claims data from the Symphony Health Solutions' Integrated Dataverse (IDV), a platform that combines clinical and demographic information with hospital, medical, and pharmacy claims for 274 million active lives in the United States. We identified 3 health plans, each from neighboring Northeastern US states, whose patient data were available in the IDV: Plan A, covering 666,212 lives, had already placed sitagliptin into tier 3 when it implemented a sitagliptin step therapy program on July 1, 2013; Plan B, covering 228,747 lives, also placed sitagliptin in tier 3, but did not implement a sitagliptin step therapy program; and Plan C, covering 667,997 lives, had placed sitagliptin in tier 2 and also did not implement a sitagliptin step therapy program (Plans B and C cover geographic areas adjacent to Plan A's coverage area). Open enrollment for the 3 plans started on October 1, 2012, and lasted 2 months. The annual coverage cycles began on January 1, 2013, for the 3 plans.

Study observations were divided into the following 3 periods: (1) January 1, 2013, through June 30, 2013, which corresponded to the 6 months before Plan A implemented its step therapy program (ie, the pre–step therapy period);
(2) July 1, 2013, through September 30, 2013, which corresponded to the 3-month period during which we assumed the new policy was fully implemented and previous sitagliptin prescriptions were exhausted; and (3) October 1, 2013, through March 31, 2014, which corresponded to the 6 months after Plan A implemented its sitagliptin step therapy program (ie, the post–step therapy period).

Patients were included in our analyses if they had been enrolled in any of the 3 health plans with continuous medical and prescription coverage between January 1, 2013, and March 31, 2014; were not enrolled in more than 1 plan; were aged ≥18 years; filled at least 1 sitagliptin prescription during the pre–step therapy period; and did not use any DPP-4 inhibitors other than sitagliptin during the pre–step therapy period (Figure 1).

**Study Measures and Analyses**

We evaluated the utilization of sitagliptin during the post–step therapy period and the utilization of other anti-diabetes medications during the pre– and post–step therapy periods. The key end point, sitagliptin use during the post–step therapy period, was defined by the presence of sitagliptin prescription claims. Patients who received prescriptions for sitagliptin during the post–step therapy period were considered to have continued using sitagliptin. Patients without any evidence of prescriptions for sitagliptin were considered to have discontinued taking sitagliptin. Other antidiabetes medication use was assessed for patients who discontinued sitagliptin during the post–step therapy period. Those patients could have switched to a preferred DPP-4 inhibitor (saxagliptin or linagliptin); discontinued all other antidiabetes medications (no prescriptions for any type of antidiabetes medication); continued other antidiabetes medications without replacing sitagliptin (did not change prescriptions of antidiabetes medications other than discontinued sitagliptin); started an SGLT-2 inhibitor, GLP-1 agonist, and/or insulin; and started other antidiabetes medications.

We also evaluated the total number of treatment classes (ie, alpha-glucosidase inhibitors, amylin analogs, biguanides, meglitinides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, and insulin) during the pre– and post–step therapy periods. Pre–step therapy antidiabetes medication use in addition to sitagliptin was also assessed (ie, sitagliptin monotherapy or combination therapy).

Patient age, sex, and several comorbid conditions based on International Classification of Diseases, Ninth Revision, Clinical Modification codes (ie, presence of benign essential hypertension, hyperlipidemia, pure hypercholesterolemia, coronary atherosclerosis of native coronary artery, unspecified obesity, shortness of breath, and unspecified chest pain) were assessed during the pre–step therapy period. Patient characteristics and pre– and post–step therapy period use of sitagliptin and other antidiabetes medications were summarized separately according to the health plan.

**Results**

We identified 2995 patients enrolled in Plan A, 751 patients in Plan B, and 394 patients in Plan C who used sitagliptin in the pre–step therapy period and met the study eligibility criteria. The patient characteristics were similar across health plans during the pre–step therapy period (Table 1).

The patients were, on average, aged 56 to 57 years, and 64% to approximately 70% were male across the 3 health plans. Although approximately 33% of patients had hypertension and approximately 25% had hyperlip-
Effects of a Sitagliptin Formulary Restriction Program

Table 1 Demographic and Clinical Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Plan A (N = 2995)</th>
<th>Plan B (N = 751)</th>
<th>Plan C (N = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>57.0 (9.3)</td>
<td>56.2 (8.5)</td>
<td>56.5 (9.3)</td>
</tr>
<tr>
<td>Male, %</td>
<td>54.7</td>
<td>55.7</td>
<td>51.0</td>
</tr>
<tr>
<td>Received insulin (pre-step therapy period), %</td>
<td>14.7</td>
<td>14.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Number of comorbid conditions, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54.7</td>
<td>55.7</td>
<td>51.0</td>
</tr>
<tr>
<td>1</td>
<td>17.4</td>
<td>18.4</td>
<td>15.5</td>
</tr>
<tr>
<td>2</td>
<td>18.1</td>
<td>16.1</td>
<td>20.8</td>
</tr>
<tr>
<td>3-7</td>
<td>9.8</td>
<td>9.4</td>
<td>12.7</td>
</tr>
</tbody>
</table>

NOTE: The pre-step therapy restriction period was January 1, 2013-June 30, 2013. SD indicates standard deviation.

Table 2 Antidiabetes Medication Use Before the Implementation of Step Therapy

<table>
<thead>
<tr>
<th>Antidiabetes medication class</th>
<th>Plan A (N = 2995)</th>
<th>Plan B (N = 751)</th>
<th>Plan C (N = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin monotherapy, %</td>
<td>10.5</td>
<td>9.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Sitagliptin combination therapy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin + metformin</td>
<td>37.2</td>
<td>39.3</td>
<td>29.7</td>
</tr>
<tr>
<td>Sitagliptin + 1 other oral antidiabetes drug</td>
<td>5.9</td>
<td>6.9</td>
<td>8.1</td>
</tr>
<tr>
<td>All other combinations (including insulin)</td>
<td>46.4</td>
<td>43.9</td>
<td>51.8</td>
</tr>
</tbody>
</table>

NOTE: The pre-step therapy restriction period was January 1, 2013-June 30, 2013. SD indicates standard deviation.

Discussion

The results of our analyses contribute to the literature on the impact of formulary restrictions by demonstrating that a step therapy program requiring a trial of a preferred DPP-4 inhibitor changed the overall use of DPP-4 inhibitors and other antidiabetes medications in patients with T2DM. We found that approximately 70% of patients enrolled in Plan A—the health plan that implemented the sitagliptin step therapy program and placed sita-

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The post–step therapy restriction period was July 1, 2013-March 31, 2014.

Table 3  Antidiabetes Medication Use After the Implementation of Step Therapy

<table>
<thead>
<tr>
<th>Antidiabetes medication use</th>
<th>Plan A (N = 2995)</th>
<th>Plan B (N = 751)</th>
<th>Plan C (N = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin use during post–step therapy period, %</td>
<td>30.1</td>
<td>49.5</td>
<td>74.6</td>
</tr>
<tr>
<td>Discontinued sitagliptin and:</td>
<td>69.9</td>
<td>50.5</td>
<td>25.4</td>
</tr>
<tr>
<td>Switched to preferred DPP-4 inhibitor</td>
<td>29.7</td>
<td>14.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Discontinued all other antidiabetes medications</td>
<td>13.5</td>
<td>14.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Continued previous antidiabetes medications</td>
<td>17.0</td>
<td>12.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Started insulin, SGLT-2 inhibitor, and/or GLP-1 agoni</td>
<td>5.0</td>
<td>3.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Received no other antidiabetes medicationsabc</td>
<td>3.8</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Started other medication</td>
<td>1.1</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Antidiabetes medication classes, mean (SD)</td>
<td>1.9 (1.2)</td>
<td>1.9 (1.2)</td>
<td>2.2 (1.1)</td>
</tr>
</tbody>
</table>

NOTE: The post–step therapy restriction period was July 1, 2013-March 31, 2014. The percentages for the discontinuing subgroups may not sum to the percent discontinued because of rounding. 17.1%, 16.6%, and 10.9% of patients in Plans A, B, and C, respectively, discontinued sitagliptin and any other antidiabetes medications used during the pre–step therapy period, whether patients were receiving sitagliptin monotherapy or sitagliptin plus other antidiabetes medications. Patients who received no other antidiabetes medications were receiving sitagliptin monotherapy during the pre–step therapy period. DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2.

Figure 2  Changes in Antidiabetes Medication Use

- **Plan A**: Started insulin, SGLT-2i, GLP-1 agonists, and sitagliptin
- **Plan B**: Started insulin, SGLT-2i, GLP-1 agonists, and sitagliptin
- **Plan C**: Continued sitagliptin

NOTE: “All medications,” “other medications,” and “previous medications” refer to antidiabetes medications.

DPP-4i indicates dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

gliptin in the third tier—who received sitagliptin during the first half of 2013 were no longer using sitagliptin during the 6-month post–step therapy follow-up period between October 1, 2013, and March 31, 2014.

Similar patients enrolled in plans without the step therapy program were much less likely to have discontinued sitagliptin treatment during the same time (approximately 51% in Plan B, which placed sitagliptin in the third tier, and 25% in Plan C, which placed sitagliptin in the second tier). As expected, these results show that more restrictive formulary policies resulted in lower utilization of sitagliptin treatment.

Although the step therapy program implemented in Plan A appeared to have reduced sitagliptin use and redirected patients to preferred DPP-4 inhibitors, it was also associated with other outcomes, such as less intensive therapy (ie, the discontinuation of sitagliptin treatment without replacement) for some patients and the discontinuation of all medications for other patients. Starting insulin treatment or taking other branded, and potentially costly, antidiabetes medications (such as GLP-1 agonists, SGLT-2 inhibitors, or insulin) was another outcome associated with the sitagliptin step therapy requirement. These findings are consistent with the expected impact of the step therapy program in Plan A and with the tiers in which sitagliptin was placed in all 3 plans.

Although patients in Plan A were more likely to discontinue sitagliptin treatment, with or without switching to another DPP-4 inhibitor, than patients in the other plans, the differences between patients in Plans A and B are much smaller than the differences between patients in Plans A and C. This is likely a result of sitagliptin’s placement in tier 3 in Plans A and B and in tier 2 in Plan C. Furthermore, these results are also consistent with how restrictive the plans were. Plan A was the most restrictive (step therapy program and sitagliptin was in tier 3), and Plan C was the least restrictive (no step therapy program and sitagliptin was in tier 2).

Our findings are also consistent with the recent literature on the effects of cost-sharing and step therapy programs. Reviews of more than 170 articles have shown that medication adherence and utilization decrease after the introduction of formulary restrictions, including the complete discontinuation of all medications.5,11,15 Despite the size of the evidence base on the effects of formulary restrictions, very few studies have focused on antidiabetes medications; however, those studies’ results are consistent with those for other conditions and other types of medications: lower copayments and medication tier reductions are related to lower healthcare costs, improved adherence, and enhanced clinical outcomes.1,13,19 Our study did not examine clinical outcomes; however, as previous studies suggest, formulary restrictions, including step therapy programs, are associated with poorer glycemic control (ie, worsening glycated hemoglobin [HbA1c] levels)18 and a lower chance of patients achiev-
ing their HbA1c goals than patients who are not managed with such programs.\textsuperscript{14}

**Limitations**
This study has several limitations that should be considered when interpreting these results. First, like other analyses of administrative data, we were unable to determine if patients consumed their filled prescriptions or if other therapies were optimized when sitagliptin was discontinued, nor could we assess clinical outcomes, such as changes in HbA1c levels.

Second, we were unable to account for other plan-related factors, such as the formulary tiers assigned to antidiabetes medications other than sitagliptin; patients’ out-of-pocket healthcare costs or their socioeconomic status, which may be related to medication adherence; coupons or patient assistance programs; or other formulary restrictions that may have been placed on antidiabetes drugs other than sitagliptin.

Third, these results are based on unadjusted analyses; however, the pre–step therapy characteristics we assessed were similar across the health plans. Furthermore, our results do account for secular trends in antidiabetes medication utilization from our use of 2 contemporaneous comparison groups.

Fourth, these analyses focused only on existing users of sitagliptin, rather than on new users of sitagliptin, during the pre–step therapy period.

Fifth, these results may not be generalizable to other health plans, including Medicare and Medicaid, or to other geographic regions.

Finally, the length of the post–step therapy period (ie, 6 months) may not have been long enough to capture the long-term effects of formulary restrictions or to rule out the impact of other factors.

**Conclusions**
T2DM is a chronic disease that is well-controlled in some patients, but not for many others. Depending on their initial HbA1c level, approximately 30% to 72% of patients with T2DM will need to add another drug within 6 months of starting antidiabetes therapy to attain their glycemic control goals.\textsuperscript{22} Policies that result in less intensive therapy for a substantial proportion of patients may come for high-risk patients than less restrictive policies.\textsuperscript{14}

Further research linking the attributes of formulary restriction policies, patient out-of-pocket costs, changes in medication use patterns, and changes in clinical outcomes is needed to understand more fully the impact of such policies. Although the step therapy program implemented in Plan A was associated with reduced sitagliptin use and redirected patients to preferred DPP-4 inhibitors, it was also associated with less intensive therapy, and with the total discontinuation of antidiabetes medications for some patients.

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**Author Disclosure Statement**
Dr Tang, Dr Shankar, and Dr Rajpathak are employees of and own stocks in Merck & Co, Inc.; Dr Huang is an employee of and owns stocks in Mallinckrodt Pharmaceuticals; Dr Liu is an employee of Merck & Co, Inc. Dr Ganz is an employee of Evidera, which provides consulting services to various healthcare companies; he is therefore precluded from receiving direct payments or honoraria from these organizations.

**References**
19. Mahoney JJ. Reducing patient drug acquisition costs can lower diabetes
Diabetes is a multifactorial disease, and 14 drug classes are currently available to manage diabetes in the United States. Despite the many diabetes resources and treatments, many patients are still above the American Diabetes Association–recommended A1C target of <7%.1

PAYERS: Newer antidiabetes drugs are expensive. To control costs, health plans have implemented formulary restrictions, such as multitier formularies and step therapy programs.2 Numerous studies have demonstrated that formulary restrictions are associated with decreased medication utilization overall, reduced adherence, and produce unfavorable outcomes.3-5 In their study in this issue, Tang and colleagues studied the effect of a step therapy program in antidiabetes medication utilization, which showed that although patients in the step therapy program were more likely to stop the preferred drug after the step therapy period compared with patients without step therapy, they are also more likely to stop the preferred medication without replacement, to switch over to a medication in a different class that is equally if not more expensive, or to stop all diabetes treatment.6

PHYSICIANS: Reducing A1C levels is correlated with a decreased risk for diabetes-related complications. Epidemiologic analysis of the UK Prospective Diabetes Study has shown that each 1% reduction in A1C is associated with significantly reduced risks for amputation, peripheral disease–related death, microvascular complications, diabetes-related death, myocardial infarction, and death from any cause.7 Equally important is the risk for hypoglycemia, and have the potential to improve metabolic consequences, such as lowering blood pressure or inducing weight loss. Physicians must also remember to support lifestyle modifications as key components to diabetes management.

PATIENTS: Diabetes management is not just about lowering blood glucose levels. It also involves lowering microvascular and macrovascular risks. Patients need to realize that controlling diabetes is a lifelong process, which requires active participation between the patients and the medical treatment team. As Tang and colleagues note, formulary restrictions and step therapy programs are common barriers in today’s healthcare system.8 Patients need to work closely with the treatment team to come up with treatment regimens that are cost-effective, doable for the patients’ lifestyle and socioeconomic backgrounds, and provide glucose-lowering effects as well as beneficial metabolic consequences.


Impact of Step Therapy Restrictions in Diabetes Care

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