Impact of Formulary Restrictions on Medication Intensification in Diabetes Treatment

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Type 2 diabetes (T2D) is a progressive disease in which most patients who begin therapy with an antihyperglycemic agent will eventually require treatment intensification to maintain glycemic control. The American Diabetes Association recommends metformin as the drug of choice for initial treatment,[1] but it does not make specific recommendations about which of many medications should be used in follow-up therapy. The most commonly used second-line agents are sulfonylureas that, like metformin, are available as inexpensive generics. However, sulfonylureas increase the risk of hypoglycemia[2,3] and have been associated with higher rates of cardiovascular disease and death.[4-8] In recent years, there has been a trend toward prescribing newer brand name–only antihyperglycemic agents, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 and -2 (GLP-1 and GLP-2) receptor agonists, resulting in sharply higher diabetes-related pharmacotherapy costs.[9,10]

Health insurers and their pharmacy benefit managers (PBMs) have reacted to growing drug spending by excluding selected high-cost brand name drugs from their formularies and by subjecting covered medications to utilization management (UM) restrictions, including prior authorization (PA), step therapy (ST), and quantity limits (QLs). Nowhere is this trend more evident than in Medicare Part D plans. In 2007, Part D plans covered, on average, 87% of all drugs on their formularies, with 18% requiring some form of UM.[11] By 2016, the share of covered drugs had dropped to 77%, with 42% requiring UM.[12]

Virtually all Part D formularies routinely exclude brand name drugs for multisource antihyperglycemic drugs, including metformin, sulfonylureas, α-glucosidase inhibitors, and thiazolidinediones (TZDs).[13] Plans also commonly restrict access to various sole-source noninsulin antihyperglycemic drugs (NIADs), including DPP-4 inhibitors, GLP-1 receptor agonists, and GLP-2 receptor agonists for which there are no direct generic equivalents. Although restricting access to brand name drugs with identical generic equivalents is noncontroversial, placing constraints on sole-source brand name drugs may lead to suboptimal therapeutic substitution in some

ABSTRACT

OBJECTIVES: To explore formulary restrictions on noninsulin antihyperglycemic drugs (NIADs) in Medicare Part D plans and to estimate the impact of formulary restrictions on use of NIADs among low-income subsidy (LIS) recipient enrollees with type 2 diabetes (T2D) undergoing treatment intensification.

STUDY DESIGN: Retrospective cohort study.

METHODS: A cohort of 2919 LIS enrollees with T2D receiving metformin monotherapy during the first quarter of 2012 who intensified treatment later in the year was tracked to assess selection of and days' supply with sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and other NIADs. We tested whether being enrolled in a Part D plan with significant formulary restrictions on sole-source brand name NIADs reduced the likelihood of receiving such agents and, if so, what the impact was on days of therapy with the second agent. A 2-part regression model was estimated with explanatory variables for plan-level restrictions and individual covariates.

RESULTS: We found that 63% of study subjects initiated a sulfonylurea, 25% a DPP-4 inhibitor, and 12% another NIAD. Greater restrictions on DPP-4 inhibitors as a class were associated with small reductions in initiation of DPP-4 inhibitors and a concomitant increase in use of sulfonylureas, but neither effect was statistically significant. For individual DPP-4 inhibitors, step therapy requirements on sitagliptin and formulary exclusion of saxagliptin resulted in significant reductions in uptake of the specific drugs but had no significant impact on total days' supply of antihyperglycemic therapy.

CONCLUSIONS: Part D formulary restrictions on sole-source brand name NIADs had little impact on patterns of treatment intensification for T2D among LIS recipients enrolled in Medicare Part D plans in 2012.

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TAKEAWAY POINTS

The objectives of this study were: (1) to examine formulary restrictions (exclusion, prior authorization, step therapy) imposed on noninsulin antihyperglycemic drugs by Medicare Part D plans in 2012 and (2) to test whether the presence and type of formulary restriction influenced choice of second-line agent among low-income beneficiaries with type 2 diabetes undergoing treatment intensification from metformin monotherapy. To avoid confounding of cost sharing and formulary restrictions, we restricted the study to low-income subsidy recipients who faced the same nominal co-pays regardless of Part D plan. Our main findings include:

- For glucagon-like peptide-1 (GLP-1) receptor agonists, 78% of all formularies analyzed excluded at least 1 of the 2 drugs available in 2012; 69% required prior authorization and 29% required step therapy.
- For dipeptidyl peptidase-4 (DPP-4) inhibitors, 22% of formularies placed no restriction on any of the 3 drugs on market in 2012, whereas 20% either excluded or required step therapy for all 3 drugs in the class.
- Generic sulfonylureas were the most commonly prescribed second-line agent (63% of subjects). Formulary restrictions had no statistically significant impact on selection of and days' supply with GLP-1 receptor agonists and DPP-4 inhibitors.

patients. The extent to which this occurs in conventional diabetes treatment is unknown.

There is a substantial literature on the impact of formulary restrictions on medication use in health plans, including several general systematic reviews,[14-17] as well as focused reviews on formulary exclusion policies,[18] ST,[19] and PA.[20] The general consensus is that formulary restrictions reduce utilization of the targeted drugs, but there is much less agreement on the impact of restrictions on costs and health outcomes. The literature is also limited in that few studies have analyzed formulary restrictions imposed on diabetes medications,[21-24] and none of these have a Medicare focus. Our study was designed to fill these gaps in the literature.

We had 2 objectives. The first was to characterize formulary coverage for NIADs in the Medicare Part D market in 2012, and the second was to test whether the presence and type of formulary restrictions influenced the choice of add-on NIADs among Medicare beneficiaries with prevalent diabetes who intensified antihyperglycemic therapy in that same year. We focused on beneficiaries prescribed metformin monotherapy early in the year who then initiated an additional NIAD later in the year. Our expectation was that formulary restrictions on sole-source brand name drugs would reduce uptake of these medications while increasing the use of generic alternatives. We also expected to find that restrictions would reduce days' supply of the restricted drug among patients who eventually did initiate the medication due to possible formulary-related delays in treatment initiation.

METHODS

Data Source and Sample Selection

Data for the study were obtained from a random 5% sample of the Medicare population in 2012 from the Chronic Condition Data Warehouse (CCW) maintained by CMS. The inclusion criteria for the sample were: (1) a T2D diagnosis code in Medicare claims prior to 2012; (2) continuous LIS enrollment with coverage under Medicare Part A, Part B, and Part D throughout 2012 or up to date of death; (3) enrolled in a single stand-alone Part D prescription drug plan (PDP); (4) treated with metformin monotherapy during the first quarter of the year; (5) filled at least 1 prescription for a DPP-4 inhibitor, sulfonylurea, or other NIAD during the final 9 months of the year; and (6) refilled at least 1 prescription for metformin following the first date the second-line agent was filled. All study subjects were linked by encrypted beneficiary identification numbers to Part D plans. We restricted the sample to PDP enrollees because beneficiaries enrolled in Medicare Advantage Part D plans did not generate Part A and B claims data necessary to characterize subjects' disease severity and comorbidities. We focused exclusively on LIS recipients because they paid the same nominal co-pays regardless of Part D plan, thereby avoiding bias associated with any correlation between formulary design and posted co-pays levied for those not receiving an LIS. The requirement that a metformin fill follow the first fill of a second NIAD ensured that the new medication represented treatment intensification rather than drug substitution.

Dependent Variables

The dependent variables of interest were utilization and days' supply of NIAD drugs prescribed for treatment intensification in the 9 months following metformin monotherapy during the first quarter of 2012. Days' supply for prescriptions extending into 2013 were truncated at December 31, 2012. The categories of NIAD drugs considered were: (1) sulfonylureas, (2) DPP-4 inhibitors, and (3) other NIADs (GLP-1 receptor agonists, TZDs, α-glucosidase inhibitors, amylinomimetics, and meglitinides). The sample sizes for specific drugs included in the third category (other NIADs) were too small to warrant separate analysis.

Assessing Formulary Restrictiveness

The CCW files include an annual end-of-year formulary file for each Part D sponsor that lists all covered medications with drug-specific UM indicators for PA, ST, and QLs. Using National Drug Codes in the CCW formulary file, we matched each plan's drug list to the 2012 edition of the FirstData Bank drug dictionary to identify all off-formulary NIADs. We then created a set of binary variables indicating whether the drugs in each pharmacologic class were excluded or subject to PA or ST (we did not investigate QLs, as these policies typically place no limit on refills). Restrictiveness measures were computed for the 2 brand name–only classes of DPP-4 inhibitors and GLP-1 receptor agonists available during the study timeframe.

We categorized formulary restrictiveness as potentially meaningful at the drug level by type of restriction (exclusion, PA, or ST) and whether all forms of the drug were subject to some type of restriction. If at least 1 form of the drug was available without restriction, we considered the drug not meaningfully restricted. We used the term potentially meaningful because we had no a priori way to assess prescriber attitudes toward therapeutic substitution of antihyperglycemic agents. We did not consider restrictions on brand name products in multisource classes as meeting the threshold of meaningfulness, as most clinicians consider generics to be equivalent to brands with identical formulations. Similarly, among DPP-4 inhibitors, if Janumet (a combination of the DPP-4 inhibitor sitagliptin and metformin) was excluded from the formulary but Januvia (sitagliptin) and generic metformin were unrestricted, then this was not considered a meaningful restriction. However, if all forms of sitagliptin were restricted, we considered that a potentially meaningful restriction. Similar classification rules were applied to saxagliptin, linagliptin, and the 2 GLP-1 receptor agonists on the market in 2012 (exenatide and liraglutide). If all drugs in a pharmacologic class were restricted, we considered the entire class to be restricted.

Other Measures

In the analytic models described below, we included a set of categorical covariates capturing individual-level variation in characteristics that could be correlated both with our formulary restrictiveness measures and with patterns of beneficiary drug utilization. These variables included demographic characteristics (age ranges, race, and sex); measures of diabetes severity (uncontrolled diabetes, short- and long-term diabetes complications, and hypoglycemia); diabetes management procedures (fasting plasma test, glycated hemoglobin test, low-density lipoprotein cholesterol test, diabetes management class, diabetic eye exam, and influenza vaccination); comorbidities common among patients with diabetes (cancer, chronic kidney disease, heart failure, and chronic obstructive pulmonary disease); and contacts with the health system (inpatient admissions and physician visits). All characteristics associated with disease states and medical utilization were captured during the 3-month baseline period during which each study subject used metformin only. **Table 1** lists all covariates, identifies how each variable was measured, and provides source notes for diagnostic codes.

Statistical Analysis

We first produced descriptive statistics for individual beneficiary characteristics by class of second-line therapy taken. Next, we characterized restrictions on DPP-4 inhibitors and GLP-1 receptor agonists across all Part D formularies applicable to the study sample in 2012, calculating the percent of beneficiaries and mean days' supply among users subject to each type of restriction. In each case, we used *t* tests to determine whether utilization rates differed significantly between formularies with and without specific restrictions. Finally, we estimated a 2-part regression model to obtain conditional effects of formulary restrictions on the probability of using DPP-4 inhibitors or other NIADs versus sulfonylureas (part 1) and mean days' supply of drugs restricted to users of sulfonylureas, DPP-4 inhibitors, and other NIADs (part 2). For the part 1 equation, we used a multinomial logistic regression comparing characteristics of subjects initiating DPP-4 inhibitors and other NIADs with those of subjects initiating sulfonylureas. For the second part of the model, we estimated 3 ordinary least squares regressions on days' supply restricted to users of DPP-4 inhibitors, sulfonylureas, and other NIADs, respectively. Variables for number of DDP-4 inhibitors with meaningful restrictions were included in all models to test for the effect of formulary restrictiveness on drug utilization patterns among study subjects (formulary restrictions on the GLP-1 receptor agonists had no measurable impact on use of other NIADs in preliminary analyses and thus were dropped in the final models).

RESULTS

Table 1 presents characteristics of the 2919 LIS recipients who met the study inclusion criteria, arrayed by choice of second-line antihyperglycemic agent following metformin monotherapy. A total of 63% (1848) initiated a sulfonylurea, 24.5% a DPP-4 inhibitor (716), and 12.2% another NIAD (355). The 3 groups were broadly similar with some notable exceptions. Specifically, a much higher proportion (53.2%) of those using other NIADs were younger than 65 years (ie, they were Medicare beneficiaries due to disability rather than age) compared with between 37% and 38% for the other 2 cohorts. Users of other NIADs also had the highest rates of uncontrolled diabetes and long-term diabetes complications.

Our analysis of 153 Part D formularies found no meaningful restrictions on metformin, sulfonylureas, α-glucosidase inhibitors, or TZDs (results not shown). Brand name drugs in these classes were almost universally excluded, but because there were generic versions available without restriction, we did not consider such exclusions to be meaningfully restrictive.

Among GLP-1 receptor agonists, either exanatide or liraglutide was off formulary in 120 formularies, subject to PA in 105 formularies, and subject to ST in 44 formularies. However, because fewer than 3% of all study subjects initiated 1 of these medications as second-line therapy, the effects on overall NIAD intensification patterns were minimal and none of the bivariate tests of GLP-1 restrictions on uptake and days' supply was statistically significant (results not shown).

All formulary restrictions on DPP-4 inhibitors that were judged to be meaningful using the criteria specified earlier are presented in the left-hand column of **Table 2**. (We have also included an **eAppendix Table** [eAppendix available at **ajmc.com**] that outlines the entire set of DPP-4 inhibitor restrictions, meaningful and not.) The top panel of Table 2 shows the extent of formulary restrictions across all DPP-4

TABLE 1. Characteristics of LIS Recipients Using Metformin by Selection of Second-Line Antihyperglycemic Drug in the Final 9 Months of 2012

Beneficiary Characteristics	% Initiating Second-Line Therapy		
	Sulfonylureas (n = 1848)	DPP-4 Inhibitors (n = 716)	Other NIADs (n = 355)
Total	63.3	24.5	12.2
Demographics			
Age, years			
<65	38.0	37.2	53.2
65-74	37.2	35.9	30.4
75-84	19.8	21.4	13.5
≥85	5.0	5.6	2.8
Female	62.0	66.1	65.1
Race/ethnicity			
White	57.5	57.7	59.7
Black	22.8	20.0	22.5
Hispanic	10.5	12.6	9.6
Other	9.2	9.78	8.2
Diabetes severity/complications[a]			
Uncontrolled diabetes[b]	12.7	17.2	20.3
Long-term complications[c]	7.9	11.0	13.5
Short-term complications[d]	0.3	0.0	0.3
Hypoglycemia[e]	0.2	0.4	0.3
Diabetes management[a]			
Fasting plasma test	4.5	4.6	6.2
A1C test	34.2	38.6	41.1
LDL-C test	28.3	31.4	37.5
Diabetes management class	0.8	1.1	1.1
Eye exam	10.7	13.8	14.4
Influenza vaccination	0.8	2.2	2.0
Comorbidities[a]			
Cancer[f]	1.8	2.2	2.0
Chronic kidney disease[g]	0.9	1.1	0.6
Chronic heart failure[h]	1.4	2.0	1.1
COPD[i]	4.0	4.6	3.1
Mental illness[j]	6.5	7.8	7.9
Health system contacts[a]			
Any hospital admission	5.8	7.7	5.1
Any physician office visit	64.6	68.3	67.3

A1C indicates glycated hemoglobin; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; *ICD-9*, *International Classification of Diseases, Ninth Revision*; LDL-C, low-density lipoprotein cholesterol; LIS, low-income subsidy; NIAD, noninsulin antihyperglycemic drug.
[a]Characteristics captured in claims during the first 3 months of 2012.
[b]Uncontrolled diabetes, *ICD-9* code 250.02.
[c]Long-term complications from diabetes, *ICD-9* codes 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x.
[d]Short-term complications from diabetes, *ICD-9* codes 250.1x, 250.2x, 250.3x.
[e]Hypoglycemia, *ICD-9* codes 250.8x, 251.0x, 251.1x, 251.2x, 962.3x.
[f]Cancer, *ICD-9* codes 140.x-239.x.
[g]Chronic kidney disease, *ICD-9* code 585.x.
[h]Chronic heart failure, *ICD-9* code 428.x.
[i]COPD, *ICD-9* codes 490.x-496.x.
[j]Mental disorders, *ICD-9* codes 290.x-319.x.

inhibitors together with statistics on initiation and days' supply for DPP-4 inhibitors, sulfonylureas, and other NIADs. Thirty-four formularies (436 study subjects) included at least 1 form of all 3 DPP-4 inhibitors with no restrictions. Sixty-one formularies (1811 subjects) restricted 1 DPP-4 inhibitor, followed by 27 restricting 2 DPP-4 inhibitors (215 subjects) and 31 restricting all 3 DPP-4 inhibitors (457 subjects). Consistent with our hypothesis, the initiation rate for DPP-4 inhibitors was generally lower among formularies restricting 2 or 3 DPP-4 inhibitors. Likewise, initiation of sulfonylureas was higher in formularies with the most restrictions on DPP-4 inhibitors, but neither of these results was statistically significant. DPP-4 inhibitor restrictions had no discernable impact on uptake of other NIADs or days' supply of any second-line agent.

The next 3 panels of Table 2 present descriptive results on initiation patterns of second-line agents as a function of formulary restrictions on individual DPP-4 inhibitors. Most formularies (122) placed no meaningful restriction on sitagliptin, whereas 29 imposed ST and 2 required PA. Initiation of sitagliptin was significantly higher ($P < .05$) in unrestricted formularies (19.7%) compared with those imposing ST (15.6%), with correspondingly fewer subjects initiating a sulfonylurea in plans with no sitagliptin restrictions (62.2%) compared with 67.8% ($P < .05$) in plans requiring ST for sitagliptin. Similar patterns were seen with respect to restrictions on saxagliptin and linagliptin, albeit the number of subjects initiating these drugs was much lower than in the case of sitagliptin. None of the drug-specific restrictions had any measurable effect on days' supply among users.

Table 3 presents findings from the multinomial regression. As in the unadjusted results, restrictions of 1 or more DPP-4 inhibitor were associated with lower initiation rates for DPP-4 inhibitors and also lower rates for other NIADs, but in neither case were the results statistically significant. The second part of the 2-part models (**Table 4**) also failed to identify any significant effects of DPP-4 inhibitor formulary restrictions on days' supply among users of DPP-4 inhibitors, sulfonylureas, and other NIADs.

TABLE 2. Characteristics of Part D Formulary Restrictions for DPP-4 Inhibitors and Associated Rates of LIS Recipient Initiation and Days' Supply With Second-Line Antihyperglycemic Drug in the Final 9 Months of 2012

Drug Class and Type of Formulary Restriction	Part D Formularies (n = 153)	LIS Recipients (n = 2919)	% LIS Recipients Initiating DPP-4 Inhibitors	Mean (SD) Days' Supply of DPP-4 Inhibitors	% LIS Recipients Initiating Sulfonylurea	Mean (SD) Days' Supply of Sulfonylurea	% LIS Recipients Initiating Other NIAD	Mean (SD) Days' Supply of Other NIAD
All DPP-4 inhibitors (n = 716)								
No restrictions	34	436	25.2	132 (76.7)	62.6	164 (199.0)	12.2	121 (74.9)
Restriction on 1 DPP-4 inhibitor	61	1811	25.6	126 (83.0)	61.7	162 (164.5)	12.7	123 (83.7)
Restriction on 2 DPP-4 inhibitors	27	215	21.4	105 (79.2)	68.4	164 (188.8)	10.2	147 (110.1)
Restriction on all DPP-4 inhibitors	31	457	21.2	134 (87.0)	67.8	149 (106.2)	10.9	126 (83.7)
Sitagliptin (n = 557)								
Unrestricted	122	2462	19.7	124 (77.0)	62.2	163 (173.4)	12.4	125 (84.3)
Formulary exclusion	0	0	0	0	0	0	0	0
Prior authorization	2	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Step therapy	29	454	15.6[b]	136 (79.0)	67.8[b]	149 (106.3)	10.8	126 (84.6)
Saxagliptin (n = 141)								
Unrestricted	86	1387	5.4	111 (66.9)	62.0	166 (181.6)	12.0	124 (79.8)
Formulary exclusion	26	990	3.4[b]	103 (63.1)	62.2	155 (151.4)	13.2	128 (89.0)
Prior authorization	1	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Step therapy	40	541	5.9	103 (67.9)	68.8[b]	156 (139.8)	10.7	119 (86.1)
Linagliptin (n = 27)								
Unrestricted	43	1296	1.5	95 (61.4)	62.0	160 (170.8)	13.1	121 (82.0)
Formulary exclusion	88	1502	[a]	[a]	63.6	161 (162.8)	11.5	125 (86.7)
Prior authorization	2	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Step therapy	20	119	[a]	[a]	73.1[b]	160 (108.2)	10.1	168 (69.4)

DPP-4 indicates dipeptidyl peptidase-4; LIS, low-income subsidy; NIAD, noninsulin antihyperglycemic drug.
[a]Cell size is less than 11 and results cannot be reported per CMS regulations.
[b]Significantly different at $P < .05$ compared with unrestricted formulary.

DISCUSSION

Our evaluation of formulary restrictions on antihyperglycemic drugs demonstrated the breadth of restrictions imposed by Part D plans in 2012. The most common type of restriction was formulary exclusion. Part D sponsors excluded virtually all brand name medications in multisource classes (metformin, sulfonylureas, α-glucosidase inhibitors, and TZDs). We did not consider these to be meaningful restrictions because generic equivalents were available without restriction in every case. Among brand name–only products, 119 of 153 formularies placed a meaningful restriction on 1 or more DPP-4 inhibitors. Formulary exclusion was the most common restriction, followed by ST. Very few plans required PA for DPP-4 inhibitors, but the practice was more common for GLP-1 receptor agonists.

Our analysis provides mixed evidence that formulary restrictions influence initiation of second-line NIADs. As hypothesized, restricting more DPP-4 inhibitors was associated with lower initiation rates for DPP-4 inhibitors and higher initiation levels with sulfonylureas, but the results were not statistically significant. At the individual drug level, ST requirements on sitagliptin reduced uptake and increased the likelihood of sulfonylurea use. Likewise, excluding saxagliptin significantly reduced uptake among the 26 formularies excluding all forms of this drug. However, the fact that these restrictions did not wholly eliminate access to either sitagliptin or saxagliptin suggests that prescribers who favored a particular drug were able to override barriers to access.

Taken together, these findings suggest that Part D plan formulary designs had little net impact on how prescribers intensified antihyperglycemic therapy for Medicare beneficiaries with diabetes in 2012. The dominant choice among prescribers was a generic sulfonylurea, followed by sitagliptin. The newer DPP-4 inhibitors, saxagliptin and linagliptin, were prescribed infrequently. We

TABLE 3. Multinomial Regression Results Showing Impact of DPP-4 Inhibitor Formulary Restrictions on Choice of Second NIAD in the Final 9 Months of 2012

Formulary Restriction Type and Beneficiary Characteristics	DPP-4 Inhibitor OR (95% CI) (reference category, sulfonylurea initiator)	Other NIADs OR (95% CI) (reference category, sulfonylurea initiator)
DPP-4 inhibitor formulary restrictions (reference, unrestricted)		
1 DPP-4 inhibitor restricted	1.03 (0.80-1.32)	0.97 (0.70-1.36)
2 DPP-4 inhibitors restricted	0.82 (0.54-1.22)	0.73 (0.42-1.26)
All DPP-4 inhibitors restricted	0.78 (0.57-1.08)	0.80 (0.52-1.23)
Demographics		
Age, years (reference, 65-74)		
<65	1.04 (0.84-1.28)	1.85 (1.41-2.43)
75-84	1.08 (0.85-1.38)	0.81 (0.56-1.18)
≥85	1.08 (0.72-1.61)	0.71 (0.35-1.41)
Female (reference, male)	1.21 (1.01-1.46)	1.31 (1.03-1.68)
Race/ethnicity (reference, white)		
Black	0.85 (0.68-1.06)	0.90 (0.67-1.20)
Hispanic	1.19 (0.89-1.57)	0.92 (0.61-1.38)
Other	1.07 (0.79-1.46)	1.06 (0.69-1.64)
Diabetes severity/complications		
Uncontrolled diabetes	1.26 (0.97-1.64)	1.43 (1.03-1.99)
Long-term complications	1.20 (0.88-1.64)	1.58 (1.08-2.33)
Short-term complications	1.00 (0.55-6.13)	0.93 (0.10-8.55)
Hypoglycemia	1.77 (0.33-9.37)	1.18 (0.11-13.23)
Diabetes management		
Fasting plasma test	0.85 (0.55-1.31)	1.22 (0.73-2.03)
A1C test	1.10 (0.84-1.44)	0.93 (0.64-1.34)
LDL-C test	0.99 (0.75-1.29)	1.59 (1.11-2.27)
Diabetes management class	1.31 (0.54-3.19)	0.95 (0.30-3.01)
Eye exam	1.22 (0.93-1.61)	1.35 (0.94-1.93)
Influenza vaccination	2.55 (1.23-5.29)	2.49 (0.98-6.38)
Comorbidities		
Cancer	1.22 (0.66-2.26)	1.30 (0.56-3.04)
Chronic kidney disease	1.13 (0.47-2.74)	0.55 (0.12-2.49)
Chronic heart failure	1.22 (0.60-2.49)	0.85 (0.27-2.61)
COPD	0.98 (0.61-1.57)	0.68 (0.34-1.36)
Mental illness	1.08 (0.75-1.55)	1.03 (0.65-1.66)
Health system contacts		
Any hospital admission	2.39 (0.27-21.29)	0.32 (0.06-1.88)
Any physician office visit	0.95 (0.75-1.20)	0.70 (0.51-0.95)

A1C indicates glycated hemoglobin; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; LDL-C, low-density lipoprotein cholesterol; NIAD, noninsulin antihyperglycemic drug; OR, odds ratio.

estimate that the reduction in prescribing of saxagliptin because of formulary exclusion was just 2 percentage points. These patterns would thus appear to have less to do with formulary restrictions than with clinician prescribing habits. Sitagliptin was the first DPP-4 inhibitor to be approved by the FDA, and later entrants had difficulty gaining market share. In our study, GLP-1 receptor agonists were the least frequently prescribed second-line brand NIADs, but they had too few initiators to reliably estimate formulary effects.

It is difficult to compare these findings with those of previous studies given the slim literature on formulary design effects in diabetes treatment. Williams et al[22] in a 2012 study found that ST restrictions on second-line NAIDs had no effect on reducing diabetes-related costs compared with unrestricted use of fixed-dose combination products. By contrast, Gamble et al[22] and Huang et al[24] found that PA requirements significantly reduced prescribing rates for TZDs and sitagliptin, respectively. The larger literature also suggests that ST[19] may have less predictable outcomes compared with PA,[20] but it is worth noting that during our study period few Part D sponsors required PA for any brand name NIADs.

A review of second-line diabetes medications conducted by an expert panel of editors for *Diabetes Care* determined that all of the medications we analyzed are clinically effective in most patients, although the risk-to-benefit profiles for newer NIADs are less well understood than those of older agents.[25] The panel concluded that choosing a specific agent for treatment intensification is less important than ensuring that such intensification is implemented as soon as clinically indicated.[25] From this perspective, our finding that formulary restrictions had little net impact on diabetes treatment intensification patterns should help assuage potential policy maker concerns that Part D sponsor formulary decisions reduce patient access to needed medications—at least with respect to treatment of patients with T2D.

Strengths and Limitations

Our focus on LIS recipients represents both a study strength and a limitation. On the one hand, we can rule out any confounding of formulary

impacts associated with cost sharing because all LIS recipients face the same nominal generic and brand co-pays regardless of formulary configuration or choice of drug. On the other hand, LIS recipients tend to cluster in basic benchmark Part D plans in which they face no monthly premiums. Non-LIS beneficiaries tend to favor enhanced plans with higher premiums and broader formulary coverage. Thus, our results cannot generalize to these beneficiaries.

Other limitations of our study design warrant mention. First, we built the study around treatment intensification in diabetes because this is a point at which many patients with diabetes first face the issue of brand name–only versus generic treatment options. Our thinking was that formulary effects would be most evident in this situation. However, the sample selection decisions we made to reduce potential confounding (limiting to LIS recipients, requiring a set period on metformin monotherapy, restricting to patients adding a second-line drug) also reduced the available sample size, which could have contributed to the lack of statistically significant findings. Our focus on LIS recipients also limits generalizability of study findings to Medicare beneficiaries who confront both formulary restrictions and cost sharing.

Second, we were blind to the administrative machinery surrounding each type of formulary restriction. Anecdotal conversations with PBMs and pharmacy and therapeutics committee members suggest that there is considerable market heterogeneity in the application and override provisions relating to all of the formulary restrictions we investigated. By contrast, the early literature on PA requirements in state Medicaid programs suggests that some state authorities aggressively used PA as a method for restricting drug access,[26,27] but the increased use of electronic health records may substantially alleviate the burden of PA on medical practices and thus reduce the disincentive to prescribe drugs on PA lists.[28]

A third methodological issue is that formulary influence may simply be diluted by the plethora of antihyperglycemic choices available to clinicians: More choices mean that any single restriction is likely to have less of an impact than it would in therapeutic classes with fewer

TABLE 4. Regression Results Showing Impact of Formulary Restrictions on Days' Supply of DPP-4 Inhibitors, Sulfonylureas, and Other NIADs Among Subjects Initiating These Drugs in the Final 9 Months of 2012

Formulary Restriction Type and Beneficiary Characteristics	DPP-4 Inhibitors		Sulfonylureas		Other NIADs	
	Estimate	*P*	Estimate	*P*	Estimate	*P*
DPP-4 inhibitor formulary restrictions (reference, unrestricted)						
1 DPP-4 inhibitor restricted	−2.65	.77	−1.57	.89	0.32	.98
2 DPP-4 inhibitors restricted	−18.90	.20	0.09	.54	20.47	.35
All DPP-4 inhibitors restricted	3.96	.73	−15.22	.27	−1.85	.91
Age, years (reference, 65-74)						
<65	−21.10	<.05	−9.55	.30	−9.41	.38
75-84	4.09	.64	19.17	.08	9.15	.55
≥85	0.49	.97	20.63	.26	16.68	.56
Female (reference, male)	0.81	.90	−8.98	.27	−0.41	.97
Race/ethnicity (reference, white)						
Black	−25.44	<.05	−1.16	.90	−13.03	.25
Hispanic	−13.87	.16	−4.41	.74	−28.40	.08
Other	−26.71	<.05	10.57	.45	−30.54	.08
Diabetes severity/complications						
Uncontrolled diabetes	−0.18	.98	−1.33	.92	−8.06	.54
Long-term complications	−7.24	.51	13.59	.37	18.21	.21
Short-term complications	0.24	.87	24.40	.74	183.75	<.05
Hypoglycemia	23.78	.64	−73.99	.45	−40.72	.64
Diabetes management						
Fasting plasma test	6.95	.65	20.52	.28	4.50	.82
A1C test	1.60	.87	−2.30	.85	18.34	.24
LDL-C test	−5.05	.60	−0.09	.99	−3.92	.80
Diabetes management class	−36.51	.23	30.22	.50	−22.63	.63
Eye exam	2.33	.81	−14.85	.25	12.65	.37
Influenza vaccination	−12.82	.55	−21.21	.62	−19.69	.57
Comorbidities						
Cancer	−11.60	.48	10.01	.73	28.01	.42
Chronic kidney disease	19.92	.40	−20.22	.63	172.97	<.05
Chronic heart failure	14.99	.48	11.38	.75	−22.30	.66
COPD	−5.42	.86	23.01	.30	−3.74	.89
Mental illness	2.23	.86	−1.74	.92	18.00	.31
Health system contacts						
Any hospital admission	−6.88	.93	84.03	.27	82.33	.21
Any physician office visit	−4.64	.57	2.62	.80	−26.30	<.05
Intercept	147.84	<.05	176.24	<.05	142.75	<.05

A1C indicates glycated hemoglobin; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; LDL-C, low-density lipoprotein cholesterol; NIAD, noninsulin antihyperglycemic drug.

alternatives. Finally, the most important caveat of all is that our findings pertain to just 1 therapeutic class used to treat a single disease within a sample of Medicare Part D plans.

CONCLUSIONS

Part D formulary restrictions on sole-source brand name NIADs had little impact on patterns of treatment intensification for T2D for LIS recipients enrolled in Medicare Part D plans in 2012. More research is necessary to understand how formulary restrictions and UM tools work in other therapeutic areas and in other organizational settings. ■

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eAppendix Table. Description of How Formulary Restrictions on DPP-4 Inhibitors Were Characterized as Potentially Meaningful[a]

Formulary Exclusions			Step Therapy			Prior Authorization			Part D Enrollees	Number of Formularies	Number of Potentially Meaningful Restrictions	Number of Formularies
Lina	Saxa	Sita	Lina	Saxa	Sita	Lina	Saxa	Sita				
No	No	No	No	No	No	No	No	No	436	34	**0**	34
No	No	No	Yes	No	No	No	No	No	1	1	**1**	61
No	No	No	No	No	No	Yes	No	No	1	1	**1**	
Yes	No	No	No	No	No	No	No	No	949	50	**1**	
No	Yes	No	No	No	No	No	No	No	860	9	**1**	
No	No	No	Yes	Yes	No	No	No	No	2	2	**2**	27
Yes	No	No	No	Yes	No	No	No	No	132	12	**2**	
Yes	Yes	No	No	No	No	No	No	No	81	13	**2**	
No	No	No	Yes	Yes	Yes	No	No	No	71	16	**3**	31
No	No	No	No	No	No	Yes	Yes	Yes	1	1	**3**	
Yes	No	No	No	Yes	Yes	No	No	No	336	10	**3**	
No	Yes	No	Yes	No	Yes	No	No	No	45	1	**3**	
Yes	Yes	No	No	No	Yes	No	No	No	2	2	**3**	
Yes	Yes	No	No	No	No	No	No	Yes	2	1	**3**	
Total									**2919**	**153**	N/A	**153**

DPP-4 indicates dipeptidyl peptidase-4; lina, linagliptin; N/A, not applicable; saxa, saxagliptin; sita, sitagliptin.

[a]Cells shaded green indicate potentially meaningful restrictions; the darker the shade of green, the greater the restriction.