Adherence, Persistence, and Health Care Costs for Patients Receiving Dipeptidyl Peptidase-4 Inhibitors

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ABSTRACT

BACKGROUND: The dipeptidyl peptidase-4 (DPP-4) inhibitors are among the newer, yet more established, classes of diabetes medications.

OBJECTIVE: To compare adherence, persistence, and health care costs among patients taking DPP-4 inhibitors.

METHODS: Claims were extracted from Humana Medicare Advantage Prescription Drug (MAPD) or commercial plans for patients aged > 18 years with ≥ 1 prescription filled for a DPP-4 inhibitor between July 1, 2011, and March 31, 2013. The first prescription claim for a DPP-4 inhibitor established the index date and index medication; 12-month pre-index and post-index data were analyzed. The Diabetes Complications Severity Index (DCSI) was used to assess a level of baseline diabetes-related comorbidities. Adherence (proportion of days covered [PDC] $\geq 80\%$) and persistence (<31-day gap) measures were compared before and after, adjusting for DCSI, pre-index insulin, age, and gender. Post-index costs (in 2013 U.S. dollars) were compared using general linear modeling (GLM) to adjust for pre-index costs, DCSI, pre-index insulin, age, and gender.

RESULTS: Based on study criteria, 22,860 patients with MAPD coverage (17,292 sitagliptin, 4,282 saxagliptin, and 1,286 linagliptin) and 3,229 patients with commercial coverage (2,368 sitagliptin, 643 saxagliptin, and 218 linagliptin) were included. For MAPD patients, the mean age was 70-72 years, and females represented 50%-52% of patients. For commercial patients, mean age was 55-56 years, and females represented 44% of patients. Clinical indicators for patients on linagliptin showed a higher comorbidity level than sitagliptin or saxagliptin cohorts (MAPD DCSI 3.0 vs 2.4 and 2.2, $P<0.001$; commercial DCSI 1.2 vs. 0.9 and 0.9, $P<0.001$); a higher use of pre-index insulin (MAPD 22% vs. 15% and 14%, $P<0.001$; commercial 18% vs. 11% and 10%, $P=0.003$); and higher mean pre-index costs (MAPD \$14,448 vs. \$11,818 and \$10,399, $P<0.001$; commercial \$13,868 vs. \$9,357 and \$8,223, $P=0.016$). For the MAPD cohort, the unadjusted PDC was lower for linagliptin patients (67%) compared with saxagliptin (72%) or sitagliptin (72%) patients ($P<0.001$). Significant differences were still seen when adjusted for covariates. Linagliptin patients were more likely to be nonpersistent (73%) than those on saxagliptin (65%) or sitagliptin (67%; $P<0.01$ for adjusted and unadjusted comparisons). For the commercial population, there were no significant differences in mean PDC between the 3 groups (linagliptin 70%, saxagliptin 72%, and sitagliptin 74%; $P=0.096$). Dichotomized comparisons of nonpersistence were significantly different (linagliptin 65%, saxagliptin 62%, and sitagliptin 57%; $P=0.010$), although upon adjustment using a Cox proportional hazard model, no significant differences were found. When controlling for other factors, post-index adjusted health care costs were similar between the medication cohorts (MAPD: sitagliptin=\$13,913, saxagliptin=\$13,651, and linagliptin=\$13,859; commercial: sitagliptin=\$11,677, saxagliptin=\$12,059, and linagliptin=\$11,163; all $P>0.25$).

CONCLUSIONS: For MAPD and commercial populations, baseline patient demographics were similar between the 3 DPP-4 inhibitor groups, but the linagliptin group may have had more complex patients (higher pre-index costs, higher DCSI, and more use of insulin). For the MAPD population,

patients on linagliptin were less adherent and persistent than patients taking sitagliptin or saxagliptin for all unadjusted and adjusted comparisons. For the commercial population, which was notably smaller, these differences were in the same direction, but not all were statistically significant. When controlling for baseline factors, 12-month post-index direct medical health care costs were similar between index DPP-4 inhibitors.

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What is already known about this subject

- Lack of adherence and persistence with antidiabetic therapy is a common problem.
- Dipeptidyl peptidase-4 (DPP-4) inhibitors have higher rates of adherence and persistence compared with sulfonylureas and thiazolidinediones.
- DPP-4 medication costs are higher than older therapies such as sulfonylureas and thiazolidinediones but have added benefits such as a lower rate of hypoglycemic events.

What this study adds

- For Medicare Advantage Prescription Drug (MAPD) plan patients, there were significant differences in adherence and persistence between the DPP-4 inhibitors, but there were mixed results for the commercial plan cohort.
- One-year total post-index health care costs were not significantly different between the 3 DPP-4 inhibitors for either cohort after covariate adjustment.
- Although adherence and persistence were found to be different for specific DPP-4 inhibitor medications in the MAPD population, this did not translate into overall cost differences, which indicates further research is needed to examine why there was not an association, and how adherence and persistence were associated with hemoglobin A1c goals and complications.

In 2012, an estimated 29.1 million adults in the United States aged 20 years and older had diabetes.¹ When poorly managed, diabetes can contribute to blindness, end-stage renal failure, nontraumatic limb amputations, cardiovascular events, and other diseases linked with premature mortality.² In addition to healthy eating and regular exercise, diabetes is largely managed with medication. However, medication

adherence and persistence among patients taking antidiabetic drugs is poor, with only 50%-60% of patients being adherent (medication possession ratio of $\geq 80\%$) or persistent over a 1-year follow-up period.³ Low-to-moderate medication adherence and suboptimal persistence can lead to compromised health outcomes (e.g., higher risk of hospitalizations, emergency room visits, increased morbidity, and premature mortality) and serious economic consequences in terms of wasted time and money.⁴⁻⁶ Estimates from 2012 show that approximately 20% of all U.S. health care dollars was spent caring for someone with diagnosed diabetes.⁷

The goal of treating diabetes is to regulate blood glucose levels, and a variety of drug classes work in different ways to lower and maintain these levels, including sulfonylureas (SUs), biguanides, meglitinides, thiazolidinediones (TZDs), bile acid sequestrants, glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose co-transporter-2 inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Weight gain and hypoglycemic events are common adverse effects of SUs and insulin. DPP-4 inhibitors help lower blood glucose levels and glycated hemoglobin (A1c) without causing hypoglycemia by preventing the breakdown of GLP-1, a naturally occurring compound in the body. GLP-1 reduces blood glucose levels in the body but is broken down very quickly, so it does not work well when injected as a drug. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow GLP-1 to remain active in the body longer, lowering blood glucose levels only when they are elevated. DPP-4 inhibitors do not tend to cause weight gain and have a neutral or positive effect on cholesterol levels.^{8,9} In addition, 2 recent studies estimate greater adherence and persistence with DPP-4s compared with SUs.^{10,11} Four DPP-4 inhibitors are currently available in the United States: sitagliptin (Januvia, approved 2006); saxagliptin (Onglyza, approved 2009); linagliptin (Tradjenta, approved 2011); and alogliptin (Nesina, approved 2013).

Two systematic reviews have assessed the cost-effectiveness of DPP-4 inhibitors compared with other antidiabetic regimens (e.g., metformin, insulin glargine, SU, and TZDs).^{12,13} In most studies reviewed, DPP-4 inhibitors were considered cost-effective relative to the comparator, but these analyses are limited by modeling long-term projections of moderate clinical benefits seen in randomized controlled trials. Higher quality studies with longer follow-up periods are needed to truly establish cost-effectiveness. A recent study by Li et al. (2014) used retrospective claims data from 2010 to 2012 to compare costs of sitagliptin with a GLP-1 agonist (liraglutide).¹⁴ Although diabetes-related pharmacy costs for patients using liraglutide were higher than costs with sitagliptin, these were offset by significantly lower diabetes-related medical costs, resulting in similar total diabetes-related costs between the 2 cohorts.

Most previous studies used models that relied on short-term randomized controlled trial data to estimate outcomes, and

few compared different medications within the same class. Since medication adherence is not as high as what is assumed in some models, costs in “everyday” practice are likely to be different. Finally, outcomes for the average patient with diabetes may not mimic those of clinical trial patients. Hence, the objective of this study was to compare real-world adherence, persistence, and health care costs of patients taking 3 different DPP-4 inhibitors.

Methods

Data Source

The data source for this study included member enrollment, medical, and pharmacy data from Humana’s administrative claims database. This included data for patients aged over 18 years with a prescription claim for any DPP-4 inhibitor filled between July 1, 2011, and March 31, 2013, who were enrolled in a commercial (nonexchange) or a Medicare Advantage Prescription Drug (MAPD) plan. The first prescription claim for a DPP-4 inhibitor established the index date and index medication; 12-month pre-index and post-index data were analyzed. The Institutional Review Board (IRB) of The University of Texas at Austin determined that this study did not meet the criteria for human subjects research as defined in the Common Rule (45 CFR 46) or Food and Drug Administration Regulations (21 CFR 56) and, therefore, did not require IRB oversight.

Selection of Patients

Patients had to have continuous plan enrollment for at least 12 months before the index date (and no DPP-4 inhibitor during this 12-month time frame) and continuous plan enrollment for at least 12 months after the index date. In addition, patients had to have at least 2 fills for the index DPP-4 inhibitor medication (i.e., index fill plus ≥ 1 refill). Also, there were too few alogliptin patients for analysis, so these were excluded.

Baseline Measurements

To assess baseline clinical differences, the Diabetes Complications Severity Index (DCSI) was used to estimate a comorbidity score. The DCSI was developed from automated clinical baseline data of a primary care diabetes cohort and has been shown to perform better than a simple count of complications to predict mortality and risk of hospitalization. It provides a disease-specific indicator for severity of disease and can be assessed using health care claims for patients with diabetes. The DCSI is composed of 7 categories of complications: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic and their severity levels (no abnormality=0, abnormality=1, and severe abnormality=2), depending on the presence and severity of the complications.¹⁵ The DCSI has been shown to be predictive of increased health care utilization for patients with diabetes.^{16,17} Other baseline measures included the use of pre-index insulin

TABLE 1 MAPD and Commercial Sample Selection and Attrition

Criteria	Patients Excluded		Patients Remaining	
	n	%	n	%
MAPD patients				
MAPD patients aged ≥ 18 years with at least 1 prescription claim for DPP-4 inhibitor during identification period of July 1, 2011-March 31, 2013			53,342	100.0
12 months continuous enrollment before index DPP-4 and no DPP-4 during this 12 months	23,216	43.5	30,126	56.5
12 months continuous enrollment after index DPP-4	2,794	5.2	27,332	51.3
At least 1 refill of index DPP-4	4,461	8.4	22,871	42.9
Exclude patients taking alogliptin	11	0.0	22,860	42.9
Final count			22,860	42.9
Commercial patients				
Commercial patients aged ≥ 18 years with at least 1 prescription claim for DPP-4 inhibitor during the identification period of July 1, 2011-March 31, 2013			9,047	100.0
12 months continuous enrollment before index DPP-4 and no DPP-4 during this 12 months	4,167	46.1	4,880	53.9
12 months continuous enrollment after index DPP-4	1,057	11.7	3,823	42.2
At least 1 refill of index DPP-4	587	6.5	3,236	35.7
Exclude patients taking alogliptin	7	0.0	3,229	35.7
Final count			3,229	35.7

DPP-4 = dipeptidyl peptidase-4; MAPD = Medicare Advantage Prescription Drug plan.

and pre-index costs. Total costs of care (plan and patient costs) for the 365-day period before the index date were calculated by summing all costs—pharmacy and medical (all claims for inpatient, outpatient, emergency, and labs)—incurred during the pre-index period with adjustment to 2013 U.S. dollars. An overall total was calculated, as well as the individual pharmacy and medical cost components.

Outcome Measurements

Treatment adherence was measured using proportion of days covered (PDC), which is defined as the proportion of days during the 365-day post-index period that the patient has any DPP-4 on hand (including any DPP-4 combination products). When assessing PDC of only 1 index medication class, any overlap is added to the days quantity. In addition to analyzing the mean PDC ratio as a continuous variable, patients who had at least 80% of DPP-4 inhibitor medications over the 12-month post-index period were classified as adherent, while those with less than 80% of medication were classified as nonadherent. Treatment persistence was also assessed and defined as the number of days on an index medication before a gap in therapy of greater than 31 days. Patients with a gap of at least 31 days were considered nonpersistent. Total cost of care (plan and patient costs) for the 365-day period following the index date was calculated by summing all costs (pharmacy and medical) incurred during the post-index period with adjustment to 2013 U.S. dollars. Similar to pre-index utilization measurements, an overall total was calculated, as well as the individual pharmacy and medical cost components.

Statistical Methods

Bivariate analyses (unadjusted) were conducted on baseline demographic and clinical variables. Categorical data (e.g., gender and pre-index insulin use) were compared using chi-square tests. Ordinal (non-normal) data (e.g., costs) were compared using Kruskal-Wallis tests, and continuous (normal) data (e.g., age) were compared using analysis of variance (ANOVA) tests. Unadjusted PDC ratios were compared using ANOVAs, and percentages of adherent patients were compared using chi-square analysis. In order to adjust for covariates, generalized linear models (GLMs) were used to compare the levels of adherence (PDC=continuous) between the 3 medication cohorts while controlling for DCSI, pre-index use of insulin, age category, and gender. GLMs provide a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than a normal distribution. Logistic regression was conducted to compare odds of patients being adherent (PDC ≥ 80%) while controlling for DCSI, pre-index use of insulin, age category, and gender.

Persistence was captured by calculating the percentage of patients who had a gap of at least 31 days in their DPP-4 use. Unadjusted percentages were compared using chi-square analysis, and logistic regression was used to compare the odds of nonpersistence while controlling for covariates. In addition, the average number of days of DPP-4 use before discontinuation was compared using ANOVAs, and Cox proportional hazard models were used to compare treatment persistence rates (days before gap=continuous) while controlling for the DCSI score, pre-index use of insulin, age category, and gender. Proportional hazards models relate the time that passes before some event occurs to 1 or more covariates that may be associated with

TABLE 2 MAPD and Commercial Baseline Demographic and Clinical Characteristics

	MAPD			Commercial		
Measure (P Values)	Sitagliptin (n = 17,292)	Saxagliptin (n = 4,282)	Linagliptin (n = 1,286)	Sitagliptin (n = 2,368)	Saxagliptin (n = 643)	Linagliptin (n = 218)
Age, years, mean (SD)						
ANOVA MAPD (P<0.001 ^a)	70.7 (±8.5) A	70.2 (±8.5) B	71.6 (±8.2) C	55.8 (±9.6)	55.5 (±9.7)	55.1 (±9.2)
ANOVA commercial (P=0.522)						
Age category, years, n (%)						
<65	2,842 (16.4)	760 (17.8)	180 (14.0)	537 (22.7)	165 (25.7)	51 (23.4)
65-69	4,285 (24.8)	1,146 (26.8)	276 (21.5)	440 (18.6)	105 (16.3)	47 (21.6)
70-74	4,674 (27.0)	1,112 (26.0)	388 (30.2)	533 (22.5)	146 (22.7)	45 (20.6)
75-79	3,018 (17.5)	724 (16.9)	235 (18.3)	540 (22.8)	150 (23.3)	51 (23.4)
80+	2,473 (14.3)	540 (12.6)	207 (16.1)	318 (13.4)	77 (12.0)	24 (11.0)
Gender, n (%)						
Chi-square MAPD (P=0.239)						
Chi-square commercial (P=0.434)						
Male	8,293 (48.0)	2,102 (49.0)	639 (49.7)	1,320 (55.7)	361 (56.1)	122 (56.0)
Female	8,999 (52.0)	2,180 (51.0)	647 (50.3)	1,046 (44.2)	282 (43.9)	95 (44.0)
Geographic region, n (%)						
Chi-square MAPD (P<0.001)						
Chi-square commercial (P<0.001)						
Northeast	401 (2.2)	59 (1.3)	22 (1.7)	4 (0.2)	0 (0.0)	0 (0.0)
Midwest	3,769 (21.8)	827 (19.3)	214 (16.6)	714 (30.2)	120 (18.7)	33 (15.1)
South	11,794 (68.2)	3,064 (71.6)	970 (75.4)	1,589 (67.1)	511 (79.5)	179 (82.1)
West	1,328 (7.7)	332 (7.8)	80 (6.2)	61 (2.6)	12 (1.9)	6 (2.8)
DCSI score, mean (SD)						
ANOVA MAPD (P<0.001 ^a)						
ANOVA commercial (P=0.001 ^a)	2.4 (±2.2) A	2.2 (±2.0) B	3.0 (±2.3) C	0.9 (±1.4) A	0.9 (±1.4) A	1.2 (±1.8) B
Insulin use pre-index, n (%)						
Chi-square, MAPD (P<0.001)						
Chi-square, commercial (P=0.003)	2,561 (14.8)	600 (14.0)	282 (21.9)	253 (10.7)	63 (9.8)	39 (17.9)
Pre-index pharmacy costs						
KW MAPD (P<0.001 ^a)						
KW commercial (P<0.001 ^a)						
Mean (SD)	\$2,925.33 (± 4,480.87)	\$2,991.91 (± 4,074.31)	\$4,078.40 (± 6,420.19)	\$2,576.02 (± 4,350.78)	\$2,940.83 (± 6,162.05)	\$4,060.37 (± 7,941.48)
Median	\$1,929.62 A	\$2,011.96 A	\$2,496.33 B	\$1,403.59 A	\$1,568.86 A	\$2,166.30 B
Pre-index medical costs						
KW MAPD (P<0.001 ^a)						
KW commercial (P=0.053)						
Mean (SD)	\$8,892.47 (± 18,882.49)	\$7,406.95 (± 14,457.14)	\$10,369.79 (± 19,105.73)	\$6,780.84 (± 24,507.26)	\$5,282.15 (± 13,625.15)	\$9,808.08 (± 39,030.05)
Median	\$2,769.98 A	\$2,630.31 B	\$3,708.71 C	\$1,364.70	\$1,314.75	\$2,224.06
Pre-index total costs						
KW MAPD (P<0.001 ^a)						
KW commercial (P=0.016 ^a)						
Mean (SD)	\$11,817.80 (± 19,974.99)	\$10,398.86 (± 15,659.18)	\$14,448.19 (± 20,800.48)	\$9,356.87 (± 25,473.46)	\$8,222.98 (± 15,182.51)	\$13,868.44 (± 41,372.86)
Median	\$8460.81 A	\$8,187.54 B	\$9,414.88 C	\$3,712.18 A	\$3,747.05 A	\$5,186.93 B

Note: all costs are in 2013 U.S. dollars.

^aFor ANOVAs and Kruskal-Wallis where P<0.05, means/medians followed by different letters (A, B, or C) are significantly different.

ANOVA=analysis of variance; MAPD=Medicare Advantage Prescription Drug plan; DCSI=Diabetes Complications Severity Index; KW=Kruskal-Wallis; SD=standard deviation.

that quantity of time; time (in days) to nonpersistence was the event modeled.

Comparisons of health care costs were conducted using a GLM with a log link and a gamma distribution (to account

for the skewed nature of health care cost data). The variables used for adjustment were the DCSI score; 12-month pre-index health care costs (medical, pharmacy, or total, as relevant to cost outcome variable for each model); pre-index use of insulin; age

TABLE 3 PDC by Index DPP-4 in MAPD and Commercial Populations

	Sitagliptin	Saxagliptin	Linagliptin
MAPD	n = 17,292	n = 4,282	n = 1,286
Mean PDC ^a (SD)	72.1 A (27.7)	72.3 A (27.8)	67.2 B (28.2)
Number adherent (PDC ≥ 80%)	8,626	2,181	533
(% adherent) ^b	(49.9)	(50.9)	(41.4)
Adjusted OR of adherence compared with linagliptin (95% CI) ^c	1.40 (1.25-1.57) P < 0.001	1.46 (1.29-1.66) P < 0.001	Reference
Commercial	n = 2,368	n = 643	n = 218
Mean PDC ^a (SD)	73.6 (27.4)	72.4 (25.9)	69.8 (26.4)
Number adherent (PDC ≥ 80%)	1,278	326	96
(% adherent) ^b	(53.0)	(51.0)	(44.0)
Adjusted OR of adherence compared with linagliptin (95% CI) ^c	1.47 (1.11-1.95) P = 0.006	1.326 (0.97-1.81) P = 0.419	Reference

^aANOVA mean values followed by different letters (A, B) are significantly different ($P < 0.001$ MAPD; $P = 0.09$ commercial); GLM controlling for age, gender, DCSI, and pre-index insulin use, also significant for MAPD and not significant for commercial ($P = 0.069$ sitagliptin vs. linagliptin, $P = 0.240$ saxagliptin vs. linagliptin).

^bChi square: $P < 0.001$ MAPD; $P = 0.012$ commercial.

^cLogistic regression controlling for age, gender, DCSI, and pre-insulin use.

ANOVA = analysis of variance; CI = confidence interval; DCSI = Diabetes Complications Severity Index; GLM = general linear modeling; MAPD = Medicare Advantage Prescription Drug; OR = odds ratio; PDC = proportion of days covered; SD = standard deviation.

category; and gender. All analyses of data were conducted using SAS version 9.4 (SAS Institute, Carey, NC) and a P value of < 0.05 .

Results

Sample

Based on study criteria, 22,860 patients were included in the MAPD cohort (17,292 sitagliptin, 4,282 saxagliptin, and 1,286 linagliptin). For the commercial cohort, 3,229 patients were included (2,368 sitagliptin, 643 saxagliptin, and 218 linagliptin). Only 18 patients had a prescription filled for alogliptin, so these patients were not included in further analysis. Table 1 shows the number excluded by each criterion.

Baseline Demographics and Clinical Characteristics

Table 2 outlines the baseline demographic and clinical characteristics and statistical comparisons for both cohorts. The average age of the MAPD cohort was 71 years, and the range by index medication was 70-72 years. About half of the patients on each medication were female, and the majority of patients resided in the South (68%-75%). Patients with the index drug linagliptin had a higher mean DCSI score (3.0) than those on sitagliptin (2.4) or saxagliptin (2.2). Patients on linagliptin also used insulin pre-index at a higher rate (22%) than those on sitagliptin (15%) or saxagliptin (14%). Pre-index costs were highest for linagliptin (pharmacy \$4.1K, medical \$10.4K), followed by sitagliptin (pharmacy \$2.9K, medical \$8.9K) and saxagliptin (pharmacy \$3.0K, medical \$7.4K).

The average age of the commercial cohort was 55 years, and the range by index medication was 55-56 years. About 44% of the patients on each medication were female, and the majority of patients resided in the South (67%-82%). Patients with the index drug linagliptin had a higher mean DCSI score (1.2) than those on sitagliptin (0.9) or saxagliptin (0.9). Patients on linagliptin also used insulin pre-index at a higher rate (18%) than those on sitagliptin (11%) or saxagliptin (10%). Pre-index costs were highest for linagliptin (pharmacy \$4.1K, medical \$9.8K), followed by sitagliptin (pharmacy \$2.6K, medical \$6.8K) and saxagliptin (pharmacy \$2.9K, medical \$5.2K).

Although baseline demographics were similar between the 3 medication groups (sitagliptin, saxagliptin, and linagliptin), clinical indicators showed a higher comorbidity level, higher use of insulin, and higher pre-index costs for linagliptin patients compared with sitagliptin or saxagliptin patients.

Adherence and Persistence

Table 3 contains results and statistical comparison for adherence comparisons. For the MAPD population, the mean PDC was lower for linagliptin patients (67%) compared with saxagliptin (72%) or sitagliptin (72%) patients. When examining the group of patients that were adherent (PDC ≥ 80%), only 41% of linagliptin patients were categorized as adherent compared with 51% on saxagliptin and 50% on sitagliptin. After adjustment for covariates, the mean PDC for patients on linagliptin was still lower than sitagliptin or saxagliptin patients ($P < 0.001$).

For the commercial population, the mean PDC was similar between medication cohorts (70% linagliptin, 72% saxagliptin, and 74% for sitagliptin). When examining the group of patients that were adherent (PDC ≥ 80), 44% of patients on linagliptin were categorized as adherent compared with 51% on saxagliptin and 53% on sitagliptin ($P = 0.012$). After adjustment, the percentage of adherent patients was lower for linagliptin patients than sitagliptin patients ($P = 0.006$).

Table 4 contains results and statistics comparisons for persistence. For the MAPD population, patients on linagliptin were more likely to have a treatment interruption of at least 31 days, that is, be nonpersistent (73% vs. saxagliptin [65%] or sitagliptin [66%]). After adjustment using a Cox proportional hazard model to control for covariates, patients taking linagliptin were still more likely to have a treatment interruption compared with the other 2 medication cohorts ($P < 0.001$).

For the commercial population, patients on linagliptin were more likely to have a treatment interruption (65% vs. saxagliptin [62%] or sitagliptin [57%]; $P = 0.010$). Upon adjustment using Cox proportion hazard methods, no significant differences were found.

A sensitivity analysis using a 60-day and 90-day gap period showed similar results (not shown). In summary, for the MAPD population, controlling for covariates, linagliptin had lower

TABLE 4 Persistence of DPP-4 Use by Index DPP-4 in MAPD and Commercial Populations

Greater than 31-Day Gap by Index Medication			
Frequency	Sitagliptin	Saxagliptin	Linagliptin
MAPD	n = 17,292	n = 4,282	n = 1,286
> 31-day gap, n (% nonpersistent) ^a	11,500 (66.50)	2,772 (64.74)	934 (72.63)
Adjusted OR of gap compared with linagliptin (95% CI) ^b	0.751 (0.661-0.852) P = 0.007	0.693 (0.604-0.0796) P ≤ 0.001	Reference
Days to gap (SD) ^c	218 days A (125)	221 days A (128)	209 days B (123)
Cox proportional hazard (95% CI) ^d	0.88 (0.82-0.94) P < 0.001	0.85 (0.79-0.91) P < 0.001	Reference
Commercial	n = 2,368	n = 643	n = 218
>31-day gap, n (% nonpersistent) ^a	1,345 (56.8)	396 (61.6)	142 (65.1)
Adjusted OR of gap compared with linagliptin (95% CI) ^b	0.71 (0.53-0.96) P = 0.004	0.86 (0.62-1.19) P = 0.860	Reference
Days to gap (SD) ^d	237 days (129)	232 days (127)	230 days (122)
Cox proportional hazard (95% CI) ^d	0.88 (0.74-1.02) P = 0.164	0.96 (0.79-1.16) P = 0.672	Reference

^aChi square: P < 0.001 MAPD, P = 0.01 commercial.

^bLogistic regression controlling for age, gender, DCSI, and pre-index insulin use.

^cANOVA means followed by different letters (A, B) are significantly different: P = 0.01 MAPD; P = 0.56 commercial.

^dCox proportional hazard regression controlling for age, gender, DCSI, and pre-index insulin use.

ANOVA = analysis of variance; CI = confidence interval; DCSI = Diabetes Complications Severity Index; MAPD = Medicare Advantage Prescription Drug plan; OR = odds ratio; SD = standard deviation.

adherence and more treatment interruption than saxagliptin or sitagliptin. For the commercial population, results trended in the same direction but were not consistently significantly different.

Health Care Costs

A summary of unadjusted mean and median post-index costs are found in Table 5. While mean pharmacy, medical, and total costs were highest for linagliptin, median costs were similar between medication groups.

Results comparing adjusted post-index costs are also found in Table 5. When adjusting mean post-index costs using a GLM to control for covariates, the mean pharmacy, medical, and total overall health care costs for MAPD patients were similar between the 3 cohorts (pharmacy \$5.2K, medical between \$8.2 and \$8.6 K, and total between \$13.7 and \$13.9K). When comparing costs for commercial plan patients, medical costs (\$6.1K-\$6.6 K) and total costs (\$11.2K-\$11.7 K) were not statistically different between medication groups, but the adjusted

mean pharmacy costs for those on sitagliptin (\$5.3K) were higher than linagliptin (\$4.6K; P < 0.001).

Discussion

This study found consistent differences in adherence and persistence across diabetes medications in an MAPD population but less consistent results in a commercial population. Given that type 2 diabetes disproportionately affects older individuals and that the sample size was larger for the MAPD cohort, the MAPD sample might have provided a more robust analysis. In this population, linagliptin adherence was 6 percentage points lower, and treatment interruption (nonpersistence) was 7 points higher, compared with saxagliptin and sitagliptin. There are presently no other published observational analyses that compare adherence of these 3 agents in the postmarketing setting. However, a 2014 study by Farr et al.,¹⁰ using 2009-2012 data from an employer-based administrative claims database, provides results that are partially relevant to the present study. They summarized data from patients taking SUs, TZDs, and 2 of the DPP-4 inhibitors (saxagliptin and sitagliptin).¹⁰ While Farr et al. found significantly better adherence in the saxagliptin cohort compared with the sitagliptin cohort, we did not find significant differences between these 2 DPP-4 inhibitors. Our study did find differences in adherence for linagliptin, which was not compared in the Farr study because of lack of sample size.

Although the MAPD linagliptin group had significantly lower adherence and persistence versus comparators in the present study, total costs for this population were not different. The lack of correlation between these 2 measures could mean several different things. One explanation is that the effect of poor adherence is not immediate, so while the lower adherence was observed during the 12-month follow-up period, the effect on comorbidities might not appear until a later date, which is outside the observation period of this study. Another possibility is that a 7% differential in adherence is not enough to produce a noticeable effect on disease management and severity. There may also be other factors responsible for the observed study results, some of which could be related to baseline differences in the 3 study groups. While baseline demographics and clinical characteristics were adjusted for in the statistical models, it is impossible to completely account for all confounding in observational database research, particularly with respect to those factors that are unknown or not able to be measured.

Limitations

There are limitations to this study to consider. The use of administrative claims has inherent bias limitations, since they are collected for reimbursement purposes. These limitations may include miscoding of diagnoses, which is important when choosing patients based on inclusion and exclusion criteria, as well as when calculating comorbidity measures. For example,

TABLE 5 MAPD and Commercial Post-index Costs

Index Medication	MAPD			Commercial		
	Sitagliptin (n = 17,292)	Saxagliptin (n = 4,282)	Linagliptin (n = 1,286)	Sitagliptin (n = 2,368)	Saxagliptin (n = 643)	Linagliptin (n = 218)
Overall health care costs						
Unadjusted mean	\$15,186.94	\$14,182.79	\$16,731.07	\$12,752.02	\$12,919.87	\$15,947.64
(SD)	(21,163.80)	(18,851.58)	(21,412.48)	(21,177.90)	(20,291.31)	(31,264.61)
Median	\$8,460.81	\$8,187.54	\$9,414.88	\$7,210.69	\$6,648.99	\$7,169.55
GLM adjusted mean ^a	\$13,912.87 Reference	\$13,651.57 P = 0.55	\$13,859.13 P = 0.87	\$11,676.62 Reference	\$12,059.10 P = 0.25	\$11,162.85 P = 0.46
Medical costs						
Unadjusted mean	\$9,616.94	\$8,591.30	\$10,438.36	\$7,096.47	\$7,376.34	\$9,946.37
(SD)	(19,563.51)	(16,991.93)	(19,464.26)	(19,423.64)	(19,174.76)	(29,035.21)
Median	\$3,094.43	\$3,013.28	\$3,368.80	\$1,730.79	\$1,572.48	\$1,699.00
GLM adjusted mean ^a	Reference \$8,608.23	\$8,200.72 P = 0.64	\$8,352.75 P = 0.40	Reference \$6,133.10	\$6,664.92 P = 0.57	\$6,267.77 P = 0.82
Pharmacy costs						
Unadjusted mean	\$5,570.04	\$5,591.49	\$6,292.71	\$5,655.55	\$5,543.53	\$6,001.27
(SD)	(5,724.53)	(5,100.61)	(6,463.2)	(5,954.57)	(5,471.36)	(6,405.00)
Median	\$4,308.01	\$4,364.95	\$4,831.17	\$4,318.28	\$4,060.52	\$4,388.49
GLM adjusted mean ^a	Reference \$5,185.46	\$5,188.88 P = 0.80	\$5,167.42 P = 0.81	Reference \$5,294.32	\$4,918.89 P = 0.09	\$4,565.99 P < 0.001 ^b

Note: All costs in U.S. 2013 dollars.

^aGLM model compared post-index costs for the index drugs adjusting for pre-index costs, DCSI, insulin use before index, age, and gender.

^bLinagliptin pharmacy costs are significantly lower than sitagliptin pharmacy costs (GLM P < 0.001).

DCSI = Diabetes Complications Severity Index; GLM = general linear modeling; MAPD = Medicare Advantage Prescription Drug plan; SD = standard deviation.

we assumed patients with ≥ 2 prescriptions for a DPP-4 inhibitor had diabetes, since we did not want to miss those with diagnosis codes outside the observation period. In addition, other potential confounding factors, such as duration of diabetes, family history, and provider characteristics were not included and may have been important covariates. Baseline clinical differences between the groups are likely to be in part because linagliptin was newer to the market compared with sitagliptin and saxagliptin, so results might have been confounded by some of these immeasurable factors.

Adherence and persistence calculations were also based on paid prescription fills, assuming that patients took their medication as directed. Both of these calculations could have been affected by the formulary status of the agents, since saxagliptin and sitagliptin were at a lower tier on the Medicare formulary during this time and were generally less expensive to patients compared with linagliptin. The effect of patient cost share on adherence is not specifically known for this study, but it is likely to have had some effect. Finally, the original research plan included measurement and comparison of A1c values, but this could not be assessed, since less than 20% of the patients had pre- and post-index levels recorded in the database.

Conclusions

Study results varied by MAPD versus commercial populations. For the MAPD and commercial plan patients, significant base-

line differences were found for patients on linagliptin. Their pre-index costs were higher; their diabetes comorbidity scores were higher; and they were more likely to be on insulin before initiating a DPP-4 inhibitor medication. Analysis of the MAPD population indicated that linagliptin patients were less adherent and persistent than the other 2 DPP-4 inhibitor groups. Commercial population results were not consistent. For the MAPD and commercial plan populations, when controlling for covariates, the overall post-index health care costs for all 3 DPP-4 inhibitor cohorts were similar. Future research should include other clinical measures, such as HbA1c and complications, in order to determine the clinical comparative effectiveness of these medications.

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