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ORIGINAL RESEARCH

Real-world medication persistence and outcomes associated with basal insulin and glucagon-like peptide 1 receptor agonist free-dose combination therapy in patients with type 2 diabetes in the US

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Background: Free-dose combination treatment with basal insulin and short-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduces hyperglycemia via complementary targeting of fasting and postprandial blood glucose levels, however, in the real world, due to injection burden and clinical inertia, the full efficacy may not be able to translate into clinical and economic benefits.

Objective: The aim of the study was to evaluate treatment persistence and associated outcomes in patients with type 2 diabetes (T2D) treated with a GLP-1 RA in free-dose combination with basal insulin.

Methods: Claims data were extracted on US adults with T2D with ≥1 prescription claim for both a GLP-1 RA and a basal insulin from July 1, 2008 to June 30, 2013, and continuous health plan coverage for 6 months prior to (baseline) and 12 months after the index date (follow-up period). Outcomes analyzed for patients stratified by treatment persistence included glycemic control, hypoglycemia, and health care costs and resource utilization. Multivariate analyses were used to examine factors associated with persistence or hypoglycemia.

Results: The analysis included 7,320 patients, of whom 16.9% were persistent with free-dose combination treatment. The median time to treatment discontinuation was 133 days. Compared with nonpersistent patients, persistent patients had greater glycated hemoglobin A1c (A1C) reductions (–0.80% vs –0.42%; P=0.032), were more likely to achieve A1C <7.0% (39% vs 22%; P<0.001), and were less likely to experience hypoglycemia (9.5% vs 6.8%; P=0.002). Persistent patients also had significantly fewer hospitalizations and shorter hospital stays. While prescription costs were significantly higher (all-cause: $14,691 vs $10,791; P<0.001; diabetes-related: $8,142 vs $5,124; P<0.001), total medical charges were significantly lower (all-cause: $28,405 vs $40,292; P=0.001; diabetes-related: $11,114 vs $15,203; P=0.003) for persistent patients compared with nonpersistent patients.

Conclusion: This retrospective claims study of US patients with T2D showed that, although persistence with concurrent GLP-1 RA and basal insulin treatment is low, improved treatment persistence is associated with greater A1C reductions and lower total medical charges.

Keywords: basal insulin, GLP-1 receptor agonist, treatment persistence, type 2 diabetes

What is already known about this subject

- Free-dose combination treatment for type 2 diabetes (T2D) with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) plus basal insulin has been used for patients who were not able to achieve A1c target with basal insulin alone. Evidence indicates that due to the complementary effects of short-acting GLP-1 RAs on postprandial

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glucose (PPG) and basal insulins on fasting plasma glucose (FPG), combination therapy represents an attractive option for treatment of patients with T2D with inadequate glycemic control with standard of care oral anti-diabetic medications or basal insulin alone.

- In order for antihyperglycemic therapies to be effective, patients must persist with therapy. Persistence with antihyperglycemic therapies, including basal insulin or GLP-1 RAs, has previously been reported to be associated with positive clinical outcomes and reduced health care utilization and costs. To date, real-world data on the duration of persistence with free-dose combination therapy of a GLP-1 RA plus basal insulin are limited.

What this study adds

- The findings from this real-world study using health care claims data show that persistence with GLP-1 RA plus basal insulin free-dose combination therapy was low (17%) over 12 months in US patients with T2D. The greatest risk of discontinuing therapy was early on in the use of combination therapy. Approximately 20% of patients had discontinued within the first month and close to 40% within the first 3 months.
- Patients with better medication persistence with GLP-1 RA plus basal insulin combination therapy had better clinical outcomes in terms of glycemic control and hypoglycemia episodes during the 12-month follow-up period. Medical resource utilization and costs were lower among treatment-persistent patients with T2D.

Introduction

Current treatment guidelines for patients with T2D recommend a patient-centered strategy based on tackling progressive worsening of glycemic control through treatment intensification. Treatment begins with lifestyle changes (eg, dietary changes, increased exercise), followed by the addition of single or multiple oral antidiabetes drugs (OADs) in order to achieve and maintain glycemic control.[1,2] As T2D progresses, deterioration in pancreatic β-cell function necessitates the use of insulin therapy to maintain glycemic control in the majority of cases.[2]

Initiation of insulin treatment using a basal insulin is recommended, usually as an addition to OADs when glycated hemoglobin A_{1c} (A1C) target is not achieved after ~3 months.[2] Basal insulins provide effective reduction of FPG levels, but increases in PPG may be inadequately controlled, and there is a risk of hypoglycemia and weight gain compared with OAD therapy alone.[3,4] Long-acting basal analog insulins such as insulin glargine 100 units/mL have proved to be safe and efficacious in long-term randomized trials and in high-quality meta-analyses,[5,6] while newer basal analog insulins, such as insulin glargine 300 units/mL and ultra-long-acting insulin degludec, may have further advantages in terms of reducing weight gain and hypoglycemia.[7,8]

GLP-1 RAs are glucoregulatory agents that enhance β-cell function and reduce body weight in patients with T2D.[9] GLP-1 RAs are a recommended option for treatment intensification in patients with T2D not achieving glycemic targets on single OAD treatment.[1,2] Clinical evidence suggests that GLP-1 RAs are associated with weight loss during treatment and a lower risk of hypoglycemia than basal insulins.[3,10–14] Both short- and long-acting GLP-1 RAs are available and have different therapeutic profiles. While long- (eg, albiglutide and exenatide LAR) and intermediate-acting (eg, liraglutide) GLP-1 RAs primarily target FPG, short-acting GLP-1 RAs (eg, exenatide and lixisenatide) primarily act through slowing gastric emptying and therefore target PPG, making them an appropriate partner of basal analog insulins that target FPG.[3,10,15] Discontinuation of GLP-1 RAs is commonly due to gastrointestinal side effects such as nausea and vomiting.

Combination treatment with a GLP-1 RA plus basal insulin has been approved by the US Food and Drug Administration and is recommended in guidelines.[2] Review of the clinical evidence indicates that owing to the complementary effects of short-acting GLP-1 RAs on PPG and basal insulins on FPG, the two types of agents represent an attractive option for intensifying the treatment of patients with T2D and inadequate glycemic control.[16,17] Studies have shown that combination treatment with a GLP-1 RA and basal insulin increases glycemic control without weight gain or increased risk of hypoglycemia.[18–21]

In order for antihyperglycemic therapies to be effective, patients must persist with therapy. Persistence with antihyperglycemic therapies, including basal insulin or GLP-1 RAs, has previously been reported to be associated with positive clinical outcomes and reduced health care utilization and costs.[22,23] To date, real-world data on persistence with a combination therapy of a GLP-1 RA plus basal insulin are limited.[24,25]

The aim of this study was to evaluate treatment persistence – and outcomes associated with persistence – with free-dose GLP-1 RA plus basal insulin combination therapy in a large population of patients with T2D identified from a medical claims database.

Methods

Study design and patients

This was a retrospective (January 1, 2008–June 30, 2014) database claims study using the Optum Clinformatics™ Data

Mart (LabRx; Eden Prairie, MN, USA) database comprising 12–13 million annual covered lives. The database included health care claims data from the health plans of patients with United Health Group commercial Administrative Services Only (ASO) insurance and fully insured patients; both medical and pharmacy coverages were included.

Included patients were aged ≥18 years with ≥1 inpatient or 2 outpatient visits (≥30 days apart) as recorded in the claim database, with a primary or secondary diagnosis of T2D (identified by ICD-9-CM diagnosis codes 250.x0 [Type II or unspecified type, not stated as uncontrolled] or 250.x2 [Type II or unspecified type, uncontrolled]);[26] had ≥1 prescription claim for both a GLP-1 RA (either short-acting exenatide or intermediate-acting liraglutide) and a basal insulin (NPH insulin, insulin glargine, or insulin detemir) between July 1, 2008, and June 30, 2013, as recorded in the claim database; and continuous health plan coverage for 6 months prior to the index date (baseline period) and for 12 months

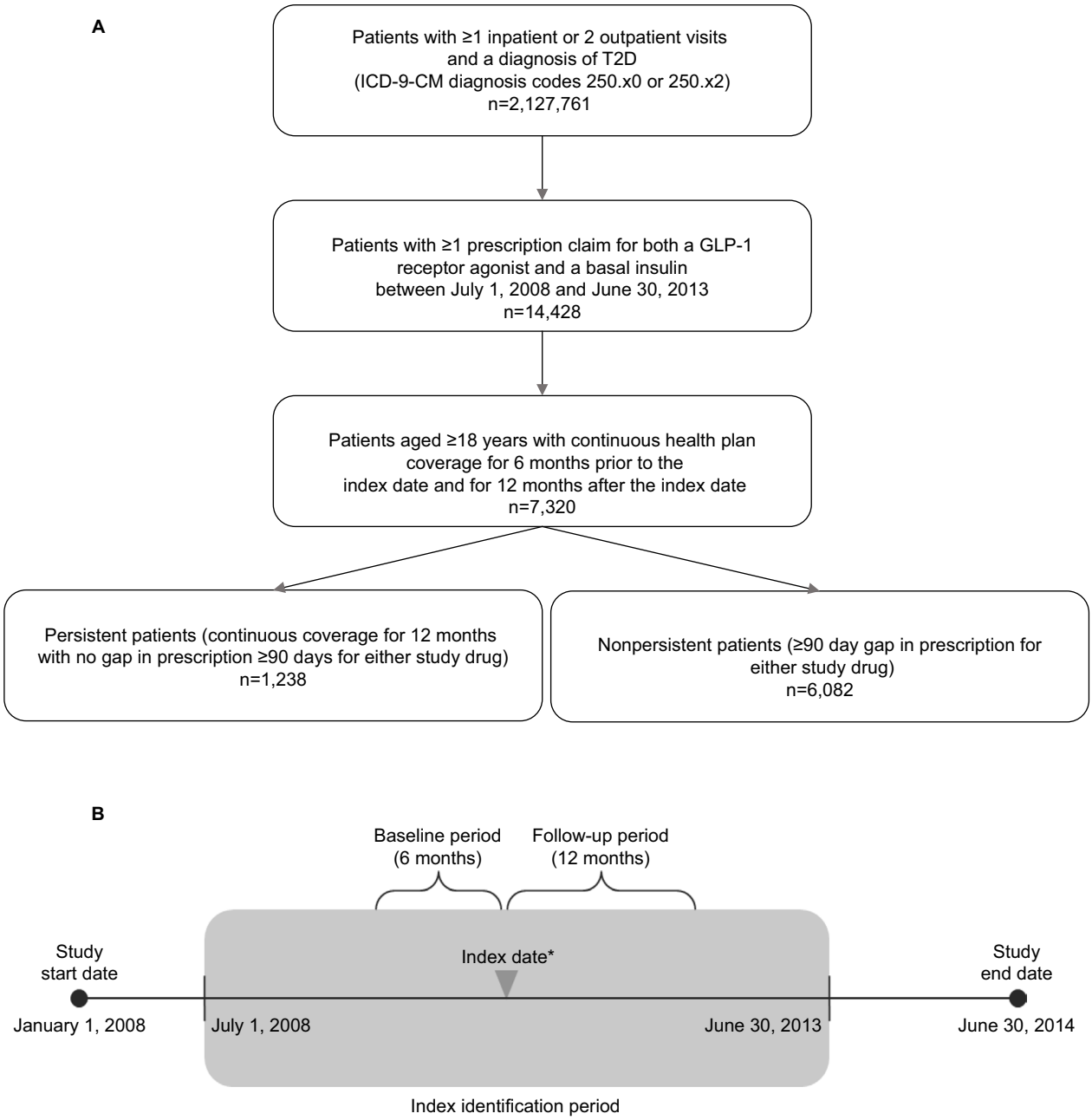

Figure 1 (A) Participant flow chart. **(B)** Schematic of study design.

Notes: *The initiation of the second drug in the combination therapy (eg, insulin plus GLP-1, or GLP-1 plus insulin) is defined as the index event, with the corresponding date as the index date. To ensure that patients received combination therapy after the index date, they were required to have ≥14 days of overlap for both therapies in the 90 days after the index date.

Abbreviations: T2D, type 2 diabetes; GLP-1, glucagon-like peptide-1.

after the index date (follow-up period; Figure 1A). The database collected data in anonymous way, retrospectively, and thus written consent was not obtained. The data used for this study also did not involve the interaction or interview with any patient and was fully de-identified. Therefore, this study is exempt from Institutional Review Board overview under the Common Rule (45 CFR ×46.101(b)(4)) and written consent under the US regulation.

Definition and measurement of combination therapy persistence

The index date for initiation of combination therapy was the date of initiation of the second therapy; ≥14 days of overlap for both therapies during the 90 days following initiation was required for inclusion. Treatment-persistent patients were defined as those patients without a prescription gap of ≥90 days in either the GLP-1 RA or the basal insulin treatment during the 12-month follow-up period. Discontinuation of either drug in the combination therapy was considered as nonpersistence. Patients were grouped into persistent and nonpersistent study cohorts (Figure 1B).

Study outcomes

A number of indices of glycemic control were compared between the study cohorts including: mean baseline A1C value, defined as the last A1C value during the baseline period or <15 days after the index date (if multiple values were available, the measurement closest to the index date was used); follow-up A1C value, defined as the last A1C value within a 3-month window at the end of the 12-month follow-up period (if multiple A1C values were recorded, the measurement closest to the end of the follow-up period was used); change in A1C, defined as the change in A1C values between baseline and follow-up; and the proportion of patients who achieved a target A1C <7.0% during the baseline and follow-up periods.

The frequency of hypoglycemia was also assessed. Hypoglycemic events were defined as any health care encounter (outpatient, inpatient, or emergency department [ED] visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia (ICD-9-CM codes: 250.8 [diabetes with other specified manifestations]; 251.0 [hypoglycemic coma]; 251.1 [other specified hypoglycemia]; or 251.2 [hypoglycemia, unspecified]).[26]

Health care resource utilization and health care costs, including all claims and associated costs incurred for inpatient, outpatient, and pharmacy services, were assessed as recorded in the claim database and compared between groups.

Statistical analysis

Descriptive statistics were used to compare the cohorts that were persistent and nonpersistent with basal insulin and GLP-1 RA combination therapy. *P*-values for unadjusted comparisons were calculated by χ^2 test or analysis of variance where appropriate. A *P*-value <0.05 was used to determine the level of statistical significance.

A multivariate regression analysis was used to control for key patient characteristics and to examine the factors associated with combination treatment persistence: the dependent variable was drug persistence (yes or no) and independent variables were patient demographics information (age; gender; region; Charlson Comorbidity Index [CCI] score; baseline diabetes-related medication usage; baseline A1C; presence of baseline hypoglycemia, hypertension, and hyperlipidemia; and baseline total health care charges).

Generalized linear regression models with appropriate data transformation and data distribution were used to evaluate the impact of persistence vs nonpersistence with basal insulin and GLP-1 RA combination therapy on A1C outcomes, all-cause medical and total health care charges, and diabetes-related medical and total health care charges. The risk of hypoglycemia was analyzed by logistic regression. For both these analyses, the dependent variables were change in A1C, risk of hypoglycemia, all-cause medical and total health care charges, and diabetes-related medical and total health care charges. The independent variables were patient drug persistence status, patient demographics information including age, gender, region, CCI score, baseline diabetes-related medication usage, baseline A1C, presence of baseline hypoglycemia, and baseline total health care charge.

Results

Baseline patient characteristics

A total of 7,320 patients met the inclusion criteria and were included in the analysis. The baseline characteristics of the study population are shown in Table 1. During the 12-month follow-up period, 1,238 patients (16.9%) were persistent and 6,082 patients (83.1%) were nonpersistent with combination treatment.

Compared with the persistent cohort, nonpersistent patients were significantly younger (57.8 years vs 56.7 years, respectively; *P*<0.001), significantly more likely to be female (43.9% vs 51.5%, respectively; *P*<0.001), and had a significantly higher CCI score (1.86 vs 2.04, respectively; *P*<0.001). Compared with the persistent cohort, nonpersistent patients were significantly more likely to have hypertension (62.9% vs 67.9%, respectively; *P*<0.001). The percentage of patients

Table 1 Baseline demographic and clinical characteristics

Characteristics	Total (n=7,320)	Persistent (n=1,238)	Nonpersistent (n=6,082)	*P*-value[a]
Age in years, mean (SD)	56.9 (10.4)	57.8 (9.4)	56.7 (10.5)	<0.001
Female, % (n)	50.2 (3,674)	43.9 (543)	51.5 (3,131)	<0.001
CCI score, mean (SD)	2.01 (1.71)	1.86 (1.70)	2.04 (1.72)	<0.001
Comorbidity, % (n)				
Hypertension	67.1 (4,909)	62.9 (779)	67.9 (4,130)	<0.001
Cardiovascular disease	71.5 (5,231)	67.0 (830)	72.4 (4,401)	<0.001
Renal disease	8.8 (644)	8.7 (108)	8.8 (536)	0.920
A1C[b], %, mean (SD)	8.89 (1.83)	8.59 (1.67)	8.94 (1.85)	0.006
Hypoglycemia during the baseline period, % (n)	5.2 (380)	3.6 (45)	5.5 (335)	0.007
GLP-1 RA % (n)				
Exenatide	23.7 (1,734)	25.2 (312)	23.4 (1,422)	0.169
Liraglutide	8.0 (586)	7.6 (94)	8.1 (492)	0.557
Basal insulin, % (n)				
Insulin glargine	39.4 (2,881)	39.8 (493)	39.3 (2,388)	0.714
Insulin detemir	12.5 (917)	12.6 (156)	12.5 (761)	0.932
NPH insulin	3.1 (226)	2.5 (31)	3.2 (195)	0.193
Concomitant antihyperglycemic medicine, % (n)				
Metformin	57.3 (4,194)	56.9 (704)	57.4 (3,490)	0.738
Sulfonylurea	36.7 (2,686)	37.8 (468)	36.5 (2,218)	0.375
DPP-4 inhibitor	16.5 (1,208)	16.8 (208)	16.4 (1,000)	0.756
Thiazolidinedione	20.4 (1,497)	22.0 (273)	20.1 (1,224)	0.126
Meglitinides	2.4 (177)	3.2 (39)	2.3 (138)	0.066
α-Glucosidase inhibitor	0.68 (50)	0.65 (8)	0.69 (42)	0.863
All-cause health care resource utilization, mean (SD)				
Number of admissions	0.09 (0.37)	0.08 (0.36)	0.09 (0.38)	0.250
Number of outpatient claims	9.53 (11.06)	8.84 (12.04)	9.66 (10.85)	0.018
Number of ED claims	0.27 (1.30)	0.18 (0.94)	0.29 (1.36)	0.010
Diabetes-related health care resource utilization, mean (SD)				
Number of admissions	0.05 (0.25)	0.04 (0.19)	0.06 (0.26)	0.017
Number of outpatient claims	4.30 (6.54)	4.07 (7.29)	4.34 (6.37)	0.185
Number of ED claims	0.06 (0.38)	0.04 (0.30)	0.06 (0.40)	0.174
All-cause health care resource costs in $, mean (SD)				
Inpatient and outpatient costs	13,529 (46,717)	10,972 (34,691)	14,049 (48,789)	0.035
ED costs	263 (2,019)	204 (2,070)	275 (2,008)	0.263
Prescription costs	3,499 (3,533)	3,793 (3,509)	3,439 (3,535)	0.001
Diabetes-related health care resource costs in $, mean (SD)				
Inpatient and outpatient costs	5,815 (28,023)	4,357 (22,326)	6,112 (29,039)	0.045
ED costs	114 (1,091)	63 (539)	124 (1,171)	0.072
Prescription costs	1,414 (1,331)	1,624 (1,493)	1,372 (1,291)	<0.001

Notes: [a]Persistent vs nonpersistent; [b]defined as the last A1C value during the baseline period or <15 days after the index date; if multiple A1C values were available, the measurement closest to the index date was used in the analysis.

Abbreviations: A1C, glycated hemoglobin A_{1c}; CCI, Charlson Comorbidity Index; DPP-4, dipeptidyl peptidase; ED, emergency department; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation.

with renal disease did not differ between persistent and nonpersistent cohorts. Nonpersistent patients also had a higher baseline mean A1C than persistent patients (persistent: 8.59% vs nonpersistent: 8.49%; *P*=0.006), and more of them had experienced hypoglycemia during the baseline period than persistent patients (3.6% vs 5.5%, respectively; *P*=0.007; Table 1).

In comparison with persistent patients, nonpersistent patients had significantly more all-cause outpatient (8.84 vs 9.66, respectively; *P*=0.018) and ED claims at baseline (0.18 vs 0.29, respectively; *P*=0.010) and more baseline diabetes-related admissions (0.04 vs 0.06, respectively; *P*=0.017). Compared with persistent patients, patients who were nonpersistent with combination therapy had higher baseline all-cause costs ($10,972 vs $14,049, respectively; *P*=0.035) and baseline diabetes-related outpatient and inpatient costs ($4,357 vs $6,112, respectively; *P*=0.045), but had lower baseline prescription costs ($1,624 vs $1,372, respectively; *P*<0.001; Table 1).

Treatment persistence and clinical outcomes

The median time to treatment discontinuation for the overall study population was 133 days (Figure 2); 22.4% of patients

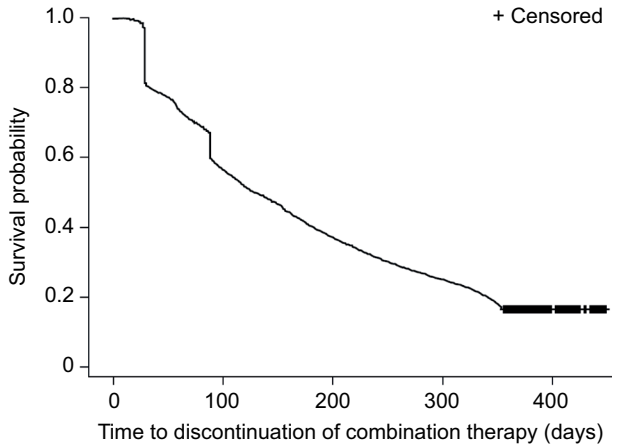

Figure 2 Kaplan–Meier curve of median time to discontinuation of combination therapy.

who discontinued did so in the first month and 39.5% discontinued within the first 3 months of treatment. Over the 12-month follow-up period, the mean reduction in A1C was significantly greater in combination-treatment-persistent patients compared with nonpersistent patients (–0.80% vs –0.42%, respectively; *P*=0.032). A significantly greater proportion of persistent patients achieved endpoint A1C <7.0% (39% vs 22%; *P*<0.001). Significantly fewer patients in the persistent cohort experienced hypoglycemia during the follow-up period (6.8% vs 9.5%; *P*=0.002).

Health care utilization and costs

Persistent patients had a significantly lower number of all-cause hospitalizations (0.18 vs 0.25; *P*=0.003) and diabetes-related hospitalizations (0.10 vs 0.14; *P*=0.006) than nonpersistent patients, respectively. Persistent patients also had shorter hospital stays than nonpersistent patients (all-cause length of stay: 0.86 vs 1.39 days, respectively; *P*=0.011; diabetes-related length of stay: 0.35 vs 0.57 days, respectively; *P*=0.014). Other total and diabetes-related health care utilizations were generally comparable between the cohorts (Table 2).

All-cause and diabetes-related total inpatient and outpatient charges were significantly lower for the persistent cohort than the nonpersistent cohort ($28,405 vs $40,292, respectively; *P*=0.001), as were total diabetes-related medical charges ($11,114 vs $15,203, respectively; *P*=0.003). Prescription costs were significantly higher in the persistent cohort than in the nonpersistent cohort (total costs: $14,691 vs $10,791, respectively; *P*<0.001; diabetes-related costs: $8,142 vs $5,124; *P*<0.001). Office visit and ED costs were comparable between the two cohorts (Figure 3).

Multivariable regression analyses

Multivariate regression analysis showed that baseline basal insulin use was associated with a higher likelihood of persistence with combination therapy (odds ratio [OR]: 2.00 [1.148, 3.484]; *P*=0.014), whereas a higher baseline A1C was associated with a lower likelihood of persistence with combination therapy (OR: 0.89 [0.817, 0.967]; *P*=0.006). Furthermore, multivariate regression analysis showed that persistence with combination therapy was associated with a greater reduction in A1C between baseline and 12-month follow-up (estimate [95% confidence interval]): (–0.57 [–0.866, –0.272]; *P*=0.002) and that higher baseline A1C measurements were also associated with greater reductions in A1C (–0.53 [–0.594, –0.464]; *P*<0.001) during the follow-up period (Table 3). Persistence with combination therapy was also a predictor of lower all-cause inpatient and outpatient medical costs during the follow-up period (estimate [95% confidence interval]: –0.24 [–0.43, –0.05]; *P*=0.013) and a predictor of lower diabetes-related inpatient and outpatient medical charges (estimate [95% confidence interval]: –0.45 [–0.66, –0.24]; *P*<0.001) during the follow-up period. Conversely, older age and baseline hypertension were predictors of higher all-cause inpatient and outpatient costs during the follow-up period (estimate [95% confidence interval]: 0.02 [–0.43, –0.05]; *P*<0.001 and 0.26 [0.10, 0.43]; *P*=0.002,

Table 2 Health care utilization in the 12-month follow-up period

Characteristics	Total (n=7,320)	Persistent (n=1,238)	Nonpersistent (n=6,082)	*P*-value[a]
All-cause, mean (SD)				
Number of admissions	0.24 (0.72)	0.18 (0.61)	0.25 (0.74)	0.003
Number of outpatient claims	22.69 (21.95)	23.01 (24.66)	22.62 (21.36)	0.571
Number of ED claims	0.67 (2.91)	0.54 (2.37)	0.70 (3.01)	0.074
Length of in-hospital stay (days)	1.30 (6.62)	0.86 (5.17)	1.39 (6.88)	0.011
Diabetes-related, mean (SD)				
Number of admissions	0.13 (0.43)	0.10 (0.37)	0.14 (0.44)	0.006
Number of outpatient claims	9.35 (11.80)	9.44 (15.04)	9.33 (11.03)	0.760
Number of ED claims	0.12 (0.65)	0.10 (0.64)	0.12 (0.66)	0.266
Length of in-hospital stay (days)	0.53 (2.76)	0.35 (1.69)	0.57 (2.93)	0.014

Note: [a]Persistent vs nonpersistent.
Abbreviations: ED, emergency department; SD, standard deviation.

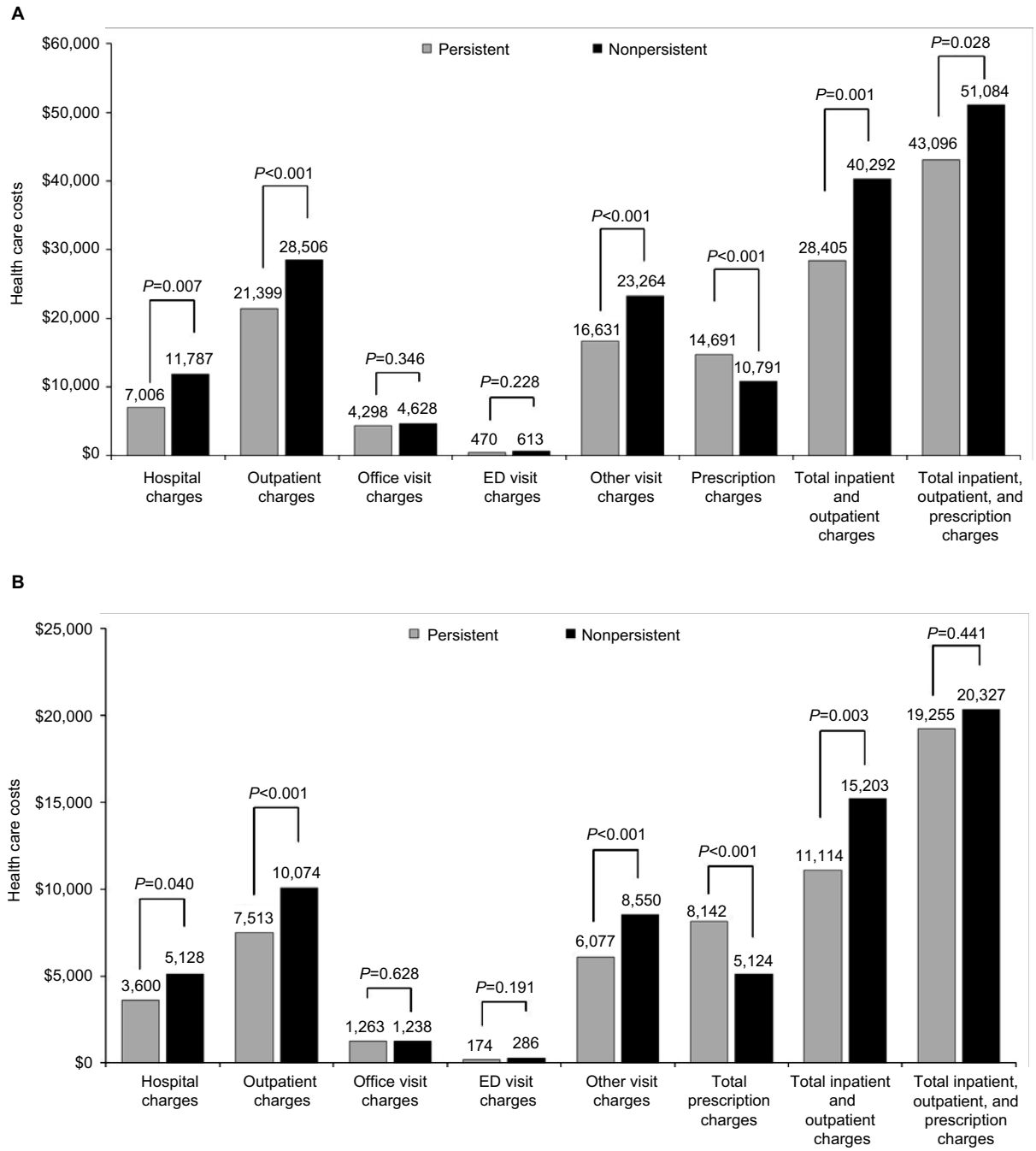

Figure 3 All-cause **(A)** and diabetes-related **(B)** health care costs over the 12 months of follow-up.
Abbreviation: ED, emergency department.

respectively). Moreover, presence of hypertension at baseline was also associated with higher diabetes-related costs (estimate [95% confidence interval]: –0.50 [0.31, 0.69]; *P*<0.001).

After controlling for key patient characteristics, the risk for hypoglycemia did not significantly differ among study cohorts (OR [95% confidence interval]: 0.552 [0.283, 1.078]; *P*=0.082). Only health plan type "other" (2.731 [1.335, 5.588]; *P*=0.006) and previous history of hypoglycemia (13.549 [8.007, 22.726]; *P*<0.001) were predictive of hypoglycemia risk.

Discussion

The findings from this real-world study using health care claims data show that persistence with GLP-1 RA plus basal insulin free-dose combination therapy was low in US patients with T2D; only 17% of patients persisted with concurrent treatment for a period of 12 months. The low

Table 3 Predictors of A1C change

Predictor	Estimate (%)	SE	95% CI	*P*-value
Persistent (vs nonpersistent)	–0.5689	0.1516	–0.8661, –0.2717	0.002
Age (per year)	–0.0028	0.0068	–0.0161, 0.0105	0.678
Female (vs male)	–0.0835	0.1166	–0.3119, 0.1450	0.474
US region (vs South)				
Midwest	0.2129	0.2206	–0.2195, 0.6453	0.335
Northeast	0.1120	0.2262	–0.3312, 0.5553	0.620
Unknown	0.3471	0.5706	–0.7712, 1.4653	0.543
West	0.1384	0.1570	–0.1693, 0.4461	0.378
Health plan type (vs point of service)				
Health Maintenance Organization	0.0040	0.1573	–0.3044, 0.3124	0.980
Exclusive Provider Organization	0.0174	0.1717	–0.3190, 0.3539	0.919
Indemnity	–0.0851	1.0411	–2.1257, 1.9555	0.935
Preferred Provider Organization	0.5761	0.3446	–0.0994, 1.2515	0.095
Other	0.0316	0.2707	–0.4990, 0.5621	0.907
CCI score (vs 0)				
1–2	–0.3561	0.3495	–1.0411, 0.3288	0.308
3–4	–0.4984	0.3634	–1.2107, 0.2139	0.170
≥5	–0.2046	0.3892	–0.9674, 0.5581	0.599
Baseline hypoglycemia (yes vs no)	0.1649	0.3050	–0.4330, 0.7628	0.589
Baseline hypertension (yes vs no)	0.0315	0.1467	–0.2560, 0.3190	0.830
Baseline lipid disease (yes vs no)	–0.0569	0.1667	–0.3837, 0.2699	0.733
Baseline A1C (per %)	–0.5293	0.0331	–0.5943, –0.4643	<0.001
Baseline usage of any OAD (yes vs no)	–0.1685	0.1435	–0.4497, 0.1126	0.240
Baseline usage of basal insulin (yes vs no)	–0.1724	0.2060	–0.5761, 0.2313	0.403
Baseline usage of any GLP-1 RA (yes vs no)	–0.3094	0.2186	–0.7379, 0.1191	0.157
Baseline all-cause total health care encounter charges (per $)	<0.0001	<0.0001	<0.0001, <0.0001	0.497

Abbreviations: A1C, glycated hemoglobin A_{1c}; CCI, Charlson Comorbidity Index; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetes drug; SE, standard error.

treatment persistence might have been due to the burden of injections, clinical inertia, as well as gastrointestinal-related adverse events.[27] In the clinical setting, the dosage of GLP-1 RAs is sometimes reduced due to adverse events during treatment. However, information about dose reductions due to adverse events is not captured by claims data, and so it was not possible to determine whether this occurred in the population studied in this analysis. Kaplan–Meier analysis indicated that the greatest risk of discontinuing therapy was early on in the use of combination therapy. Approximately 20% of patients had discontinued treatment within the first month and close to 40% within the first 3 months. However, patients who were persistent with GLP-1 RA plus basal insulin combination therapy had significantly improved glycemic control, and significantly fewer treatment-persistent patients reported hypoglycemia episodes during the 12-month follow-up period, which might be due to the effect of basal insulin or a reduction in food intake accompanying the appetite loss associated with GLP-1 RA administration. Total hospitalization rates and both all-cause and diabetes-related total medical costs were lower among treatment-persistent patients. Multivariate regression analyses supported these observations, showing that persistence with combination therapy is predictive for a greater reduction in A1C, and lower total and diabetes-related medical costs.

These findings add to and support previously published data from randomized clinical studies showing that the addition of a GLP-1 RA to basal insulin therapy leads to improvements in glycemic control.[16,18–21,28–30] Evidence from both a systematic literature review of observational and clinical practice studies (N=5,000) and a meta-analysis of clinical trials indicates that combination therapy with basal insulin and GLP-1 RAs improves glycemic control without weight gain and with no increased risk of hypoglycemia.[16,31]

Importantly, our observations extend the limited current knowledge and understanding of the clinical and economic impact of treatment persistence with concurrent use of GLP-1 RA plus basal insulin combination therapy in insured US patients with T2D in clinical practice. Real-world clinical outcomes associated with combination treatment have been reported in two previous retrospective studies that used national US health claims data.[24,25] Both studies reported that A1C levels significantly reduced from baseline during combination therapy with exenatide and glargine with no

increase in hypoglycemia, and without weight gain, irrespective of the order in which the two agents were prescribed.[24,25]

One of these studies, using the Integrated Health Care Information Services Impact database, reported that persistence with combined treatment for 1 year was observed in one-third of patients; this rate is higher than that observed in our study (16.9%), which may be explained in part by the difference in methodology used to determine treatment persistence. A greater proportion of patients remained on insulin glargine therapy but discontinued exenatide, possibly due to the relative inconvenience of twice-daily injections of exenatide or due to adverse gastrointestinal effects associated with exenatide.[24] Similarly, in our study, baseline basal insulin use was a predictor of combination treatment persistence, indicating that patients adding GLP-1 RA therapy were more likely to discontinue during follow-up, although data on the type of discontinued medicine were not available.

As previously noted, rates of discontinuation were higher during early combination therapy with the addition of a GLP1 RA. Adverse gastrointestinal events are more common in the early stages of treatment, especially during the first 8 weeks of treatment, with GLP-1 RAs[32,33] and hypoglycemia is likely to be more common during the titration phase early in insulin treatment.[34] However, there was no association between baseline hypoglycemia, which predicted follow-up hypoglycemia, and discontinuation rate. Neither was there any difference in the proportion of patients using OADs, such as sulfonylureas, which are likely to cause hypoglycemia in the persistent and nonpersistent cohorts. It may be that increased treatment complexity and additional injections are driving discontinuation, as suggested in the previous study by Levin et al,[24] and new-generation combined insulin/GLP-1 RA pens may offer a solution to this putative driver of discontinuation.[35] Additionally, if gastrointestinal adverse events are also driving discontinuation of combination therapy, these could be mitigated by the use of fixed-ratio titratable combinations due to their slow titration of the GLP-1 RA, thereby increasing persistence.

Previously, persistence with liraglutide has been shown to be associated with significantly lower medical costs compared with those who discontinued treatment, as well as with improved A1C outcomes.[22] Similarly, patients who were persistent with basal insulin treatment over a 1-year period showed greater reductions in A1C and lower health care utilization than those who were not persistent.[23] However, to our knowledge, the present study is the first to demonstrate that persistence with GLP-1 RA plus basal insulin combination treatment is associated with improved glycemic control, lower health care resource use, and lower medical costs.

As discussed above, data from clinical studies support the therapeutic potential of combining basal insulin and GLP-1 RAs in one single injection. Novel therapies that combine basal insulin and GLP-1 RAs in one single fixed-ratio injection, recently approved by the US Food and Drug Administration, will potentially benefit patients with clinical efficacy and improved medication persistence and patient experience.

In pivotal clinical trials, fixed-ratio combination of Insulin Glargine and Lixisenatide (iGlarLixi), has demonstrated superior A1c reduction compared with insulin glargine alone with no increased risk of hypoglycemia or weight gain. During the continued determination of the safety and efficacy of such combinations, the effects of the comorbidities of cardiovascular disease and chronic kidney disease (CKD) should be borne in mind.[36]

Limitations

The study had several limitations. As this is a retrospective database analysis, no causal relationship between persistence and outcomes can be established, and the data may not be representative of all patients with T2D. The reasons for treatment discontinuation in this study are unknown. This study used prescription data to determine discontinuation rates, but prescription orders do not mean that the medication was taken by patients as directed. Also, the methodology did not include patients who restarted medication after a prescription gap of ≥90 days. Claims data also do not provide detailed information about treatment, such as the order of administration of drugs, or dose reductions due to adverse events. Furthermore, not all episodes of hypoglycemia may have been reported in the database, resulting in underreporting bias. Finally, claim database records may be subject to coding error, but they are generally considered as high-quality data sources and have been used in many research studies.

Conclusion

In conclusion, the real-world outcomes data from this retrospective database study indicate that important health economic as well as clinical benefits are associated with persistence to combined GLP-1 RA and basal insulin treatment in patients with T2D. Further large-scale observational studies are required to explore the reasons for the low persistence rates observed with this novel combination treatment.

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Author contributions

Study concept and design were developed by Fan and Lin. Lin and Lingohr-Smith collected the data and performed the analyses. All authors contributed toward the data analysis, interpretation of the data, drafting and critically revising the manuscript.

All authors had full access to all the data in the study and agree to be accountable for all aspects of the work. Lin is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure

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