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BRIEF REPORT

Relationship between treatment persistence and A1C trends among patients with type 2 diabetes newly initiating basal insulin

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This study examines the relationship between glycated haemoglobin (A1C) levels and treatment persistence with, or time to discontinuation of, basal insulin in patients with type 2 diabetes (T2D) newly initiating insulin. Claims data were extracted from the Optum Clinformatics database from January 2010 to June 2015. Adult patients with T2D initiating insulin glargine 100 U/mL (Gla-100) or insulin detemir (DET) with ≥1 A1C measurement during 12-month baseline and 18-month follow-up periods were included. Patients with a refill gap of >90 days were considered non-persistent; otherwise, patients were considered persistent with insulin. The main outcome was A1C, measured closest to the end of each quarter during the follow-up period. A total of 3993 of 109 934 patients met the inclusion criteria (43.0% persistent; 57.0% non-persistent). Persistent patients were older (54.7 vs 52.7 years; $P < .001$), were more likely to be male (59.4% vs 54.4%; $P = .002$), and had significantly lower mean unadjusted A1C values at 18 months (8.26% vs 8.60%; $P < .001$) and quarterly. Only 43.0% of adults initiating basal insulin persisted with treatment for 18 months, with earlier discontinuation associated with higher A1C.

KEYWORDS

basal insulin, type 2 diabetes

1 | INTRODUCTION

The American Diabetes Association[1] and the International Diabetes Federation[2] recommend maintaining a glycated haemoglobin (A1C) level <7% in most patients with type 2 diabetes (T2D). However, for patients to achieve and maintain the A1C target, they must adhere to, and persist with, treatment regimens.

Basal insulin discontinuation rates are high among patients with T2D.[3–6] Low persistence with insulin therapy has important consequences, increasing the risk of hyperglycaemia and, consequently, diabetes-related complications.[7] Elevated A1C levels are strongly predictive of diabetes-related complications[8] and increased diabetes-related health care costs.[9]

Patients who maintain good adherence to diabetes drugs have significantly fewer hospitalizations or emergency department visits than those who are non-adherent.[10] Furthermore, non-adherent patients who become adherent have significantly fewer hospitalizations or emergency department visits than those who remain non-adherent.[10] Significantly fewer all-cause and diabetes-related hospitalizations and lower associated costs have also been linked to improved persistence.[6,11] However, there are only limited data to show how persistence affects glycaemic control over time.[11]

The primary objective of this retrospective claims-data analysis was to examine the relationship between treatment persistence with basal insulin and A1C levels over time in patients with T2D newly initiating insulin. A secondary objective was to examine the association between the timing of basal insulin discontinuation and A1C levels.

2 | METHODS

2.1 | Data source and time point definitions

Claims data for commercially insured and Medicare populations were extracted from the Optum Clinformatics database from January 1,

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2010 to June 30, 2015 ("study period"). Patients with a first claim for insulin glargine 100 units/mL (Gla-100) or insulin detemir (DET) ("index date") between January 1, 2011 and December 31, 2013 ("index period") were included. The 12-month pre-index period was defined as the "baseline period" and the 18-month post-index period as the "follow-up period."

2.2 | Patient selection

Inclusion criteria were: ≥1 pharmacy claim for Gla-100 or DET during the index period; primary or secondary diagnosis of T2D (International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification [ICD-9-CM codes: 250.x0 or 250.x2; ICD-10-CM code: E11]) during the study period; continuous enrollment in a health plan during baseline and follow-up periods; ≥18 years of age at index date; ≥1 oral antidiabetes drug (OAD) and/or glucagon-like peptide-1 receptor agonist (GLP-1 RA) and no insulin therapy during the baseline period; and ≥1 A1C measure during baseline and follow-up periods.

Patients with an insulin refill gap of >90 days during the follow-up period were considered to have discontinued treatment and were classified as "non-persistent." This cohort was further divided into 3 subgroups based on time from initiation to discontinuation: 0 to 6, 7 to 12 or 13 to 18 months.

2.3 | Baseline characteristics

Baseline demographics (age, gender, geographic location), data concerning OAD use, concomitant medications, hypoglycaemic events and all-cause healthcare utilization were extracted. The A1C level closest to the index date was used as the baseline value. Comorbidities (chronic pulmonary disease, gastrointestinal disturbances, cancer, hypertension, hyperlipidaemia, neuropathy, nephropathy, retinopathy, obesity, mental illness) and Charlson Comorbidity Index (CCI) scores were obtained using ICD-9-CM codes.

2.4 | Outcome measures

The primary outcome was the A1C measurement closest to the end of each 3-month period (quarter) during the follow-up period. In the secondary analysis, differences in A1C were examined for patients in each cohort who discontinued insulin after 0 to 6, 7 to 12 or 13 to 18 months.

2.5 | Statistical analyses

All variables were compared descriptively between cohorts. Categorical variables are reported as numbers and percentages and continuous variables as means and standard deviations. T-tests and Pearson $\chi 2$ tests were used for statistically significant differences between cohorts.

Generalized estimating equation (GEE) regression models that extend a generalized linear model to account for the correlation of repeated A1C measurements and missing data were applied to compare A1C levels between cohorts (primary analysis) and to compare persistent patients and those who discontinued after 0 to 6, 7 to 12 and 13 to 18 months of follow-up (secondary analysis). Time as a categorical variable, cohort indicator, and the interaction between time and cohort were controlled in the model in addition to patient demographics and baseline clinical characteristics. Adjusted mean and *P* values were calculated for A1C levels during each quarter during the follow-up period.

All statistical analyses were conducted using SAS v9.3 (Cary, North Carolina, USA).

3 | RESULTS

3.1 | Baseline characteristics

We identified 109 934 patients with ≥1 Gla-100 or DET claim(s) during the index period, among whom 3993 met the inclusion criteria. Of these, 1715 (43.0%) were persistent and 2278 (57.0%) non-persistent with basal insulin use (Figure S1).

At baseline, persistent patients were older (mean 54.7 vs 52.7 years; $P < .001$) and more likely to be male (59.4% vs 54.4%; $P = .002$) (Table S1). Baseline comorbidities were mainly comparable between cohorts, although gastrointestinal disturbances were less frequent among persistent patients (21.1% vs 25.9%; $P < .001$), while cancer (6.8% vs 4.7%; $P = .006$) and hyperlipidaemia (85.7% vs 83.1%; $P = .021$) were more common among persistent patients. Patients in both cohorts had similar mean CCI scores (0.78 vs 0.75; $P = .487$).

Persistent patients had slightly lower average baseline A1C levels (9.62% vs 9.71%; $P = .177$) (Table S1), received a greater number of OADs (mean 2.4 vs 2.2; $P < .001$) and were significantly more likely to receive statins and angiotensin-converting enzyme inhibitors than non-persistent patients. The incidence of hypoglycaemia at baseline was significantly lower for persistent patients (3.4% vs 4.8%; $P = .024$). Persistent patients were less likely to have had a hospital stay during the baseline period (10.7% vs 16.6%; $P < .001$).

3.2 | A1C levels during follow-up

Persistent patients had a significantly lower mean unadjusted A1C than non-persistent patients by the end of the follow-up period (8.26% vs 8.60%, respectively; $P < .001$) (Figure 1A).

After adjusting for patient demographics and clinical characteristics, the GEE adjusted model showed that persistence with basal insulin was associated with significantly lower A1C compared to non-persistence at 6, 9, 12, 15 and 18 months post-index (Figure 1B). Older age and any hospital stay were associated with a significantly lower quarterly A1C. Use of dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 RAs, and residence in the southern region of the USA was associated with higher quarterly A1C ($P < .05$). Hyperlipidaemia was controlled for but was not statistically significant.

3.3 | A1C levels by time to discontinuation

A total of 73.4% of non-persistent patients discontinued basal insulin within the first 6 months of follow-up; the percentage of patients discontinuing treatment decreased over time (21.1%, Months 7–12 and 5.6%, Months 13–18). Average time to treatment discontinuation was 134.0 days, with discontinuation time being 69.3 days for patients who discontinued within 0–6 months, 284.3 days for those

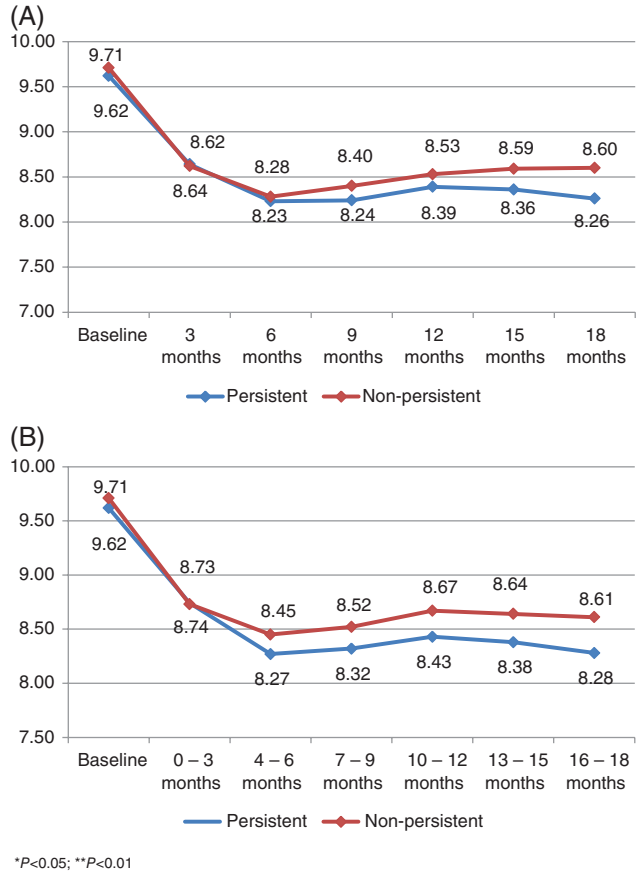

FIGURE 1 Descriptive (A) and GEE-adjusted (B) quarterly A1C trends *P < .0; Abbreviations: A1C, glycated haemoglobin A1c; GEE, generalized estimating equation

who discontinued within 7–12 months, and 417.2 days for those who discontinued within 13–18 months. Unadjusted quarterly mean A1C was consistent with adjusted values (Table S2).

In the adjusted model, non-persistent patients who discontinued basal insulin within the first 6 months of follow-up had higher A1C than persistent patients at Months 6, 9, 12, 15 and 18 (Table 1). There were no significant differences in A1C between persistent patients and those who discontinued during Months 7 to 12 or 13 to 18. Biannual A1C data comparing persistent and non-persistent cohorts were similar to quarterly A1C data (Figure S2).

The GEE model was examined separately in age groups 18 to 64 years and ≥65 years. The impact of persistence on A1C over time was significant for the age group 18 to 64 years, but not for the group ≥65 years (Figure S3). However, because of the small sample size for the group ≥65 years, the power to detect a difference may be limited (N = 143 persistent vs N = 136 non-persistent).

4 | DISCUSSION

Despite the benefits of treatment persistence, 57.0% of patients in this analysis were non-persistent with insulin therapy within 18 months of initiation, with the majority discontinuing within the first 6 months (73.4% of those who discontinued; 41.8% of all patients).

This study shows that patients who were persistent with basal insulin therapy had significantly lower A1C at 18 months compared with non-persistent patients. This was the case for both the unadjusted and GEE-adjusted regression model results. After controlling for baseline demographics and comorbidities, an additional accumulative decrease in A1C was observed at most of the 3-month time points during the 18-month follow-up period.

Discontinuation within 6 months of initiation was associated with significantly higher adjusted A1C levels at 6 months vs levels in persistent patients. For the subgroups who discontinued during Months 7 to 12 or 13 to 18 post-index, GEE modeling showed no significant differences in A1C compared to the persistent cohort at any time point. This probably demonstrates the negative association between discontinuing basal insulin at an early stage of therapy and glycaemic control, although it should be noted that the subgroup that discontinued during Months 13 to 18 post-index was relatively small, which could have affected the robustness of the results for this subgroup. Further large-scale observational studies are needed to clarify the underlying mechanisms.

4.1 | Limitations

In observational studies, causality of drug effect on outcome cannot be established, and a relationship can only be implied. Retrospective observational claims analyses may also be subject to selection bias and confounding. However, this was addressed in the GEE-adjusted regression model, which considered potential confounders while controlling for baseline demographics and comorbidities.

Treatment substitution post discontinuation may have attenuated some of the differences between persistent and non-persistent cohorts. To address patients who discontinued basal insulin and restarted at a later date, medication possession ratios (MPRs) of basal insulin were calculated for patients who persisted and those who discontinued basal insulin within 0 to 6, 7 to 12 and 13 to 18 months of initiation. MPR was based on the total number of days' supply of Gla-100 or DET divided by the number of days in the 18-month follow-up period. Stopping and restarting insulin therapy would produce an inconsistency in MPRs; however, the MPRs were consistent with the insulin discontinuation time. MPRs over the 18-month follow-up period were 0.74 for persistent patients and 0.25, 0.45 and 0.56 for patients who discontinued during Months 0 to 6, 7 to 12 and 13 to 18, respectively. This suggests that patients restarting insulin during the follow-up period did not influence the findings of this study.

Claims data are collected for payment purposes; therefore, such data may have limitations for clinical research, for example, by underreporting baseline comorbidities. Interpretation may also be affected by diagnosis-coding errors. Further, the filing of prescription claims is not indicative of medication usage and the claims do not capture the use of medication obtained "over the counter" or provided as samples by the physician.

Further analysis of treatment patterns or pathways may shed light on the heterogeneity of the patient population initiating basal insulin and their diverse outcomes. Temporal relationships among hypoglycaemia, persistence and glycaemic control could be further examined to illustrate the impact that hypoglycaemia has on persistence, and on achieving glycaemic control over time.

TABLE 1 Multivariate adjusted three-monthly mean A1C levels of persistent and non-persistent patients based on time of discontinuation

		Non-persistent					
	Persistent (N = 1715)	Discontinued during Months 0 to 6 (N = 1671)		Discontinued during Months 7 to 12 (N = 480)		Discontinued during Months 13 to 18 (N = 127)	
Quarter	Mean A1C (%)	Mean A1C (%)	*P* value*	Mean A1C (%)	*P* value*	Mean A1C (%)	*P* value*
Q1 (Months 0–3)	8.74	8.69	.520	8.83	.460	8.95	.334
Q2 (Months 4–6)	8.27	8.48	.002	8.34	.501	8.44	.334
Q3 (Months 7–9)	8.32	8.57	<.001	8.41	.418	8.22	.584
Q4 (Months 10–12)	8.43	8.75	<.001	8.39	.754	8.70	.171
Q5 (Months 13–15)	8.38	8.73	<.001	8.41	.787	8.34	.873
Q6 (Months 16–18)	8.28	8.68	<.001	8.51	.059	8.21	.789

Abbreviation: A1C, glycated haemoglobin A1c.

*vs persistent.

In conclusion, in this study 57.0% of patients discontinued basal insulin within 18 months of initiation. Persistent patients had significantly lower A1C than non-persistent patients; those who discontinued within 6 months of initiation had poorer A1C outcomes than those who discontinued later in the follow-up period. This highlights the importance of early persistence with basal insulin therapy for glycaemic outcomes in patients with T2D.

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Conflicts of interest

F. L. Z., R. P. and C. P. are Sanofi employees and stock/shareholders. Y. W., L. X. and N. V. are employees of STATinMED Research, under contract with Sanofi. F. Y. is an employee of Sanofi. L. M. serves as a consultant and advisory board member for Sanofi-Aventis and Novo Nordisk.

Author contributions

F. L. Z. contributed to designing the study, acquiring the data and writing the first draft of the manuscript. C. P. and F. Y. contributed to designing the study and acquiring the data. L. X., Y. W. and N. V. contributed to acquiring the data. R. P. contributed to designing the study. All authors contributed to the data analysis and interpretation, and critically reviewed the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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