Greater persistence and adherence to basal insulin therapy is associated with lower healthcare utilization and medical costs in patients with type 2 diabetes: a retrospective database analysis

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ABSTRACT
Introduction We aimed to assess persistence and adherence to basal insulin therapy, their association with all-cause healthcare resource utilization (HCRU) and direct medical costs, and predictors of persistence and adherence in adults with type 2 diabetes.

Research design and methods A retrospective cohort study was conducted with US adults with type 2 diabetes initiating basal insulin therapy between January 1, 2016, and December 31, 2018, using IQVIA PharMetrics Plus claims data. Persistence and adherence were assessed during 1 year post-initiation per previous definitions. Demographic/clinical characteristics were assessed during the 1 year pre-initiation. Inverse probability of treatment weighting (IPTW) was used to adjust for confounding variables. Post-IPTW, all-cause HCRU and direct medical costs were assessed during the first-year and second-year post-initiation by persistence and adherence status. Multivariable logistic regression was used to identify predictors of persistence and adherence.

Results The final sample comprised 64,953 patients; 56.8% demonstrated persistence and 41.9% demonstrated adherence. Patients demonstrating persistence and adherence were significantly less likely to have a hospitalization than patients demonstrating non-persistence or non-adherence, respectively. In the second-year post-initiation, total mean all-cause direct medical costs per patient were lower for patients demonstrating persistence and significantly lower for patients demonstrating adherence. Prior use of both oral and injectable antidiabetic medication predicted persistence and adherence compared with patients with only prior oral antidiabetic medication use (persistence OR 1.50 [95% CI, 1.44 to 1.57]; adherence OR 1.48 [95% CI, 1.42 to 1.55]).

Conclusions Persistence and adherence to basal insulin was associated with fewer hospitalizations and lower direct medical costs.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Persistence and adherence to basal insulin therapy may impact healthcare utilization and medical costs for adults with type 2 diabetes.

WHAT THIS STUDY ADDS
⇒ Persistence and adherence to basal insulin was associated with fewer hospitalizations and lower direct medical costs. Prior use of oral and injectable antidiabetic medication was associated with greater persistence and adherence compared with prior use of oral antidiabetic medication alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Efforts to improve persistence and adherence to basal insulin therapy may reduce the healthcare burden of type 2 diabetes.

PLAIN LANGUAGE SUMMARY
Some people with type 2 diabetes use insulin to manage their blood sugar, but many struggle to take insulin as prescribed by their doctors. We wanted to find out if patients who took insulin as prescribed had different levels of healthcare use and medical costs than patients who did not take insulin as prescribed in the first year after starting insulin treatment. Using a health insurance claims database, we determined whether a patient obtained insulin continuously (persistence) and was picking up the correct amount of insulin as prescribed by their doctor (adherence) throughout the year. We also measured patients’ baseline characteristics before starting insulin treatment to identify predictors of patient persistence and adherence. Among 64,953 patients, 56.8% showed persistence and 41.9% showed adherence to basal insulin. Patients showing persistence and adherence had fewer hospitalizations than patients showing non-persistence and non-adherence. Total average direct medical costs in the second year of insulin treatment were lower for patients showing persistence.
and adherence (persistence vs non-persistence, $14,777 vs $15,491; adherence vs non-adherence, $14,303 vs $15,661). Patients who previously used oral and injectable diabetes medications were more likely to show persistence and adherence compared to patients who previously used oral diabetes medications alone. These results suggest that taking insulin as prescribed can lead to lower rates of healthcare use and lower direct medical costs for patients with type 2 diabetes.

INTRODUCTION

In 2022, the US Centers for Disease Control and Prevention Diabetes Surveillance System estimated 37.3 million adults (11.3% of the adult population) had diabetes, of these, approximately 95% had type 2 diabetes. Despite advances in diabetes care, many patients are not seeing improvements in reaching their individual care goals. Many people with type 2 diabetes struggle to take their antidiabetic medications as prescribed; this can contribute to worse health outcomes, increased healthcare resource utilization (HCRU), and increases in medical costs.

Several studies have demonstrated the importance of persistence with, and adherence to, antidiabetic medications to improve glycemic control in patients with type 2 diabetes but less is known about basal insulin therapy specifically. The American Diabetes Association and European Association for the Study of Diabetes recommend healthcare professionals consider optimizing medication adherence when selecting antidiabetic medications. Adequate management of type 2 diabetes, including insulin therapy which many patients will require, can prevent, or delay, complications associated with diabetes. There is a need for current data on basal insulin persistence and adherence and their impact on HCRU and costs, which may help guide research and clinical efforts.

In this study, we aimed to assess patient persistence and adherence to basal insulin therapy and their association with all-cause HCRU and direct medical costs in the year after initiation. Additionally, we assessed HCRU and medical costs in the second year following initiation of basal insulin therapy, clinical predictors of patient persistence and adherence and the impact of patient persistence and adherence to basal insulin on glycemic control.

RESEARCH DESIGN AND METHODS

Study design and data source

An observational, retrospective cohort study was conducted among adult patients with type 2 diabetes initiating basal insulin therapy in the USA. This study was a retrospective, non-interventional study using de-identified patient data and thus exempt from review by an Institutional Review Board. This study was carried out in accordance with the Declaration of Helsinki and the de-identified patient data contained within the PharMetrics Plus database complies with the Health Insurance Portability and Accountability Act.

The overall study period was January 1, 2015, to December 31, 2019, which was chosen to avoid the potential impact of the COVID-19 pandemic on insulin adherence/persistence and economic outcomes. See online supplemental figure 1 for an overview of the study design.

The study used IQVIA’s PharMetrics Plus longitudinal health plan database of adjudicated medical and pharmacy claims for national and subnational health plans and self-insured employer groups comprising commercially managed patients. The PharMetrics Plus database does not include uninsured patients but does include some patients with commercially managed Medicare or Medicaid plans. IQVIA’s Ambulatory Electronic Medical Records (AEMR) database was also used to investigate exploratory objectives (which required patient hemoglobin A1c (HbA1c) data) and to report relevant descriptive data not available in the claims database (eg, weight and body mass index (BMI)). Linkage to AEMR was not required and the data were used as available.

Study population

Eligible patients were required to have prescription claim for basal insulin (including ultra-long-acting and long-acting basal insulin) and were identified in the PharMetrics Plus database during the study selection window from January 1, 2016, to December 31, 2018.

Patients were included if they were ≥18 years of age at index (date of first basal insulin claim) and had continuous enrollment in a health plan for ≥360 days pre-index and post-index. Patients were required to have ≥1 diagnosis for type 2 diabetes on a confirmatory medical claim in the pre-index period.

Patients were excluded if they had ≤1 claim for any insulin or insulin-related accessory in the 360-day pre-index period, ≥1 claim for a non-basal insulin (eg, bolus) on the index date, ≥1 claim for a basal insulin (generic molecule level and/or marketed product level) other than the basal insulin on the index date, ≥1 claim for a fixed-dose basal/glucagon-like peptide-1 receptor agonist combination on the index date, ≥1 diagnosis on a medical claim for type 1 diabetes, ≥1 diagnosis on a medical claim for secondary diabetes in the pre-index period without a claim for long-term insulin therapy in the post-index period, or ≥1 diagnosis on a medical claim for pregnancy or gestational diabetes in the pre-index or post-index periods. Patients were also excluded if they had incomplete data coverage or data quality issues including evidence of Medicare Cost plan coverage; prescription benefits only; missing sex, region, or payer type; or with missing quantities of days’ supply of basal insulin prescriptions during the post-index period.

Additional inclusion criteria were applied to patients included in the secondary and exploratory outcomes analyses. To assess 2-year post-index outcomes, patients were required to have ≥720 days of continuous enrollment in the same health plan post-index. To assess...
changes in patients’ HbA1c levels, patients were required to have ≥1 HbA1c record in the AEMR database near the index date (index date±90 days) and ≥1 HbA1c record near the end of the 360 days post-index (index date+360 days (±90 days)).

**Study outcomes and measures**

Patient baseline demographic and clinical characteristics were evaluated during the 1-year pre-index period. The primary outcomes of the study were the assessment of persistence and adherence to basal insulin during the first-year post-index, and the assessment of HCRU and associated medical costs during the first and second years post-index. All-cause HCRU was measured by the proportion of patients using inpatient, emergency room (ER), or outpatient services within the year post-index and by mean utilization per patient in a persistence or adherence cohort. Direct all-cause medical costs were reported as per patient costs in a persistence or adherence cohort. Costs were converted to 2021 US dollars using the medical component of the Consumer Price Index.

Patients were considered persistent up until their discontinuation date (if they discontinued basal insulin) or the end of the 1-year post-index period. Patient discontinuation of insulin was determined using a previously published method. For each patient basal insulin claim, an allowed refill gap was defined based on the drug, delivery method, and quantity of drug prescribed (online supplemental table 1). The allowed refill gap was set as the 90th percentile of the time to next refill based on index claims. Non-persistence was defined as when the time-to-refill exceeded the allowed refill gap.

Adherence was also evaluated using a previously published method. Adherence was reported as the proportion of days covered over the 360-day follow-up period and calculated as the number of days with drug on-hand, divided by the days in the follow-up period. The numerator was capped at 360. Number of days with drug on-hand was only counted once if there were multiple prescriptions for basal insulin prescribed with overlapping days’ supply. An adjustment factor was made to the days’ supply when calculating adherence because insulin use depends on a variety of factors. For each insulin drug and delivery combination, the adjustment factor was calculated to be the median time between basal insulin claims divided by the median pharmacy-reported days’ supply (online supplemental table 2). Patients were included in the adherence cohort if their proportion of days covered was ≥80% of the follow-up period.

The secondary objective included identifying predictors of persistence and adherence among patients initiating basal insulin therapy via logistic regression models using pre-index demographic and clinical information. The exploratory objective involved comparing changes in HbA1c between persistence cohorts and adherence cohorts in the first-year post-index. If patients had more than one HbA1c record in the index period (±90 days), we used the HbA1c record closest to the index date. If patients had more than one HbA1c record at the end of the post-index period (index date+360 days (±90 days)), the HbA1c record closest to 360 days post-index was chosen (index date+360 days).

**Statistical analysis**

Descriptive statistics are reported for all study measures. Categorical measures are presented as frequency and percentage. Continuous and count variables are presented using mean, SD, median, and IQR. When relevant, continuous variables were grouped into appropriate intervals. Missing values are presented as separate categories and missing data was not imputed. Patients were required to have values for critical variables for the analysis (eg, age, sex, region, and days’ supply on post-index basal insulin prescription claims). Race, ethnicity, and sex reported in the IQVIA databases were self-reported by patients.

Cohorts were balanced using an inverse probability of treatment weighting (IPTW) with stabilized weights approach, which controls for baseline differences between multiple groups while preserving the total number of patients included in each group. Separate IPTW balancing was conducted for adherence versus non-adherence cohort comparisons and persistence versus non-persistence cohort comparisons, respectively. The IPTW cohort balancing used 22 variables (online supplemental table 3). Analysis of HCRU and costs at 2 years post-initiation required distinct IPTW balancing among the subset with 2-year follow-up data which used 23 variables (online supplemental table 3). Variables were chosen if they were considered clinically relevant and/or if they were unbalanced between the cohorts. IPTW balancing was assessed pre-IPTW and post-IPTW by calculating the standardized mean difference (SMD) between cohorts across baseline confounding variables. Baseline characteristics were considered well-balanced for a baseline variable if the (absolute) SMD between groups was <10%.

After IPTW balancing, HCRU and costs were compared between persistence and non-persistence cohorts, and adherence and non-adherence cohorts. For comparisons of HCRU and costs post-IPTW, pairwise dependent comparisons between persistence and non-persistence cohorts, and adherence and non-adherence cohorts, were conducted using weighted $\chi^2$ tests for categorical variables and weighted t-tests (mean) for continuous variables.

For the analysis of persistence and adherence predictors, logistic regression models were developed which included clinically relevant variables following review of pre-index imbalances, association reports, and collinearity. The logistic regression models included age, sex, region, health plan type, index year, index product, Diabetes Complications Severity Index (DCSI) score (a score from 0 to 15 with higher scores indicating greater frequency and/or severity of diabetes complications), dyslipidemia, hypertension, antidiabetic medication use,
pre-index hospitalizations (yes/no), pre-index ER visits (yes/no), and pre-index outpatient physician office visits (yes/no) as independent covariates.

Analysis of HbA1c was conducted on a small sample of patients due to the limited number of patients with relevant data, without IPTW balancing. The exploratory analysis on HbA1c change was conducted both without statistical adjustments and with statistical adjustments using a generalized linear model controlling for age, sex, and baseline HbA1c as independent covariates. Statistical analysis was conducted using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). The level of statistical significance for all analyses was set at p<0.05.

Data and resource availability
The underlying data sets used in this study are available with permission from IQVIA, but restrictions apply to the availability of these data, which were used under license for the current study and therefore are not publicly available.

RESULTS
Patient demographics
Initially, 854,199 patients were identified in the claims database as having ≥1 prescription claim for basal insulin in the selection window. A total of 64,953 patients met all study eligibility criteria (online supplemental figure 2). The baseline demographic and clinical characteristics for the group with 1-year follow-up pre-IPTW balancing are shown in online supplemental table 4 and online supplemental table 5, respectively.

Overall, 36,901 patients (56.8%) persisted with basal insulin therapy over the 1-year post-index period. The remaining 43.2% of patients (n=28,052) discontinued basal insulin, on average, 197 days post-index. Overall, 27,208 patients (41.9%) adhered to basal insulin over the 1-year post-index, while 37,745 (58.1%) of patients did not adhere to basal insulin therapy over the 1-year post-index.

A total of 33,285 patients had at least 2 years of follow-up; 19,198 and 14,087 were included in the persistence and non-persistence cohorts, respectively, while 13,752 and 19,533 were included in the adherence and non-adherence cohorts, respectively. Full demographic and clinical characteristics for the subgroup with 2 years of follow-up pre-IPTW are shown in online supplemental table 6 and online supplemental table 7, respectively. Full demographic and clinical characteristics for the subgroup with 2 years of follow-up post-IPTW are shown in online supplemental tables 8 and 9, respectively. For the exploratory analyses, 864 patients had both pre-index and post-index HbA1c records (persistence and non-persistence, 522 and 342; adherence and non-adherence, 399 and 465), and 1,050 had ≥2 post-index HbA1c records (persistence and non-persistence, 651 and 399; adherence and non-adherence, 493 and 557).

Overall, post-IPTW, 36,909 and 28,058 patients were included in the persistence and non-persistence cohorts, respectively; 27,212 patients were included in the adherence cohort and 37,758 patients in the non-adherence cohort (table 1). Patients were well-balanced across characteristic demographic and clinical variables post-IPTW adjustment as shown by SMD of <0.1 (see select baseline characteristics table 1) and propensity score distribution plots (online supplemental figure 3). See online supplemental table 10 for additional baseline clinical characteristics post-IPTW, for the group with 1-year follow-up.

There was considerable overlap between the persistence and adherence cohorts. For the post-IPTW sample, 68.7% (n=25,344) of persistence patients were also adherent, while 94.4% (n=25,687) of adherence patients were also persistent; 39.0% (n=25,344) of the overall sample were both persistent and adherent.

Healthcare resource utilization in the year following insulin initiation
All-cause HCRU in the year following insulin initiation is shown in figure 1A–B. Persistence and adherence cohorts were significantly less likely to have a hospitalization or ER visit than non-persistence and non-adherence cohorts, respectively (both p<0.0001). Among patients with at least one all-cause hospitalization, mean total hospitalization days were lower for persistence (10.4) versus non-persistence (13.8, p<0.0001) cohorts and adherence (10.1) versus non-adherence (13.2, p<0.0001) cohorts. The proportion of patients with ≥1 all-cause ER visit was significantly lower for persistence and adherence cohorts compared with their reference cohorts (figure 1A–B).

Persistence and adherence cohorts were significantly more likely to have at least one physician office visit, laboratory test, radiology examination, outpatient surgery, and outpatient ancillary service than cohorts demonstrating non-persistence and non-adherence, respectively (figure 1A–B). Persistence and adherence cohorts had a higher mean number of all-cause physician office visits in the year following insulin initiation (persistence vs non-persistence, 14.0 vs 13.7; adherence vs non-adherence, 14.1 vs 13.7; both p<0.05). Full details of all-cause HCRU over year 1 are shown in online supplemental table 11.

Healthcare costs in the year following insulin initiation
Healthcare costs in the year following basal insulin initiation are shown in figure 1C–D. Total mean all-cause acute care costs (inpatient and ER) were lower for the persistence and adherence cohorts compared with their reference groups (both p<0.0001); individually, inpatient and ER costs were also lower (p<0.0001 and p<0.01). Mean all-cause outpatient medical costs were similar between persistence and adherence cohorts and their reference groups in the year following insulin initiation (figure 1C–D). Costs for specific outpatient medical services were similar for persistence and adherence cohorts and their reference groups except for mean all-cause radiology costs, which were lower for adherence
Table 1  Baseline patient demographic and clinical characteristics by basal insulin persistence and adherence status post-inverse probability of treatment weighting balancing, group with 1-year follow-up

<table>
<thead>
<tr>
<th>Metric*</th>
<th>Basal insulin persistence status</th>
<th>SMD</th>
<th>Basal insulin adherence status</th>
<th>SMD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Persistance</td>
<td></td>
<td>Non-Persistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adherence</td>
<td></td>
<td>Non-Adherence</td>
<td></td>
</tr>
<tr>
<td>Total patients, n (%)</td>
<td>36,909 (100)</td>
<td>28,058 (100)</td>
<td>27,212 (100)</td>
<td>37,758 (100)</td>
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<tr>
<td>Age, years</td>
<td>55.1 (10.5)</td>
<td>55.2 (10.9)</td>
<td>−0.0017</td>
<td>55.2 (10.5)</td>
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<tr>
<td>Median (IQR)</td>
<td>56 (12)</td>
<td>56 (13)</td>
<td></td>
<td>56 (13)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td>18–34 years</td>
<td>1,186 (3.2)</td>
<td>923 (3.3)</td>
<td>0.0466</td>
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<tr>
<td></td>
<td>35–44 years</td>
<td>4,043 (11.0)</td>
<td>3,294 (11.7)</td>
<td>2,919 (10.7)</td>
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<tr>
<td></td>
<td>45–54 years</td>
<td>11,249 (30.5)</td>
<td>8,573 (30.6)</td>
<td>8,340 (30.6)</td>
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<td>55–64 years</td>
<td>15,553 (42.1)</td>
<td>11,230 (40.0)</td>
<td>11,447 (42.1)</td>
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<td>≥65 years</td>
<td>4,879 (13.2)</td>
<td>4,038 (14.4)</td>
<td>3,625 (13.3)</td>
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<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>20,625 (55.9)</td>
<td>15,663 (55.8)</td>
<td>0.0012</td>
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<tr>
<td></td>
<td>Female</td>
<td>16,284 (44.1)</td>
<td>12,395 (44.2)</td>
<td></td>
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<td>Geographical region, n (%)</td>
<td>Northeast</td>
<td>6,389 (17.3)</td>
<td>4,863 (17.3)</td>
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<td></td>
<td>Midwest</td>
<td>9,027 (24.5)</td>
<td>6,853 (24.4)</td>
<td>6,647 (24.4)</td>
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<td></td>
<td>South</td>
<td>16,701 (45.3)</td>
<td>12,691 (45.2)</td>
<td>12,307 (45.2)</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>4,792 (13.0)</td>
<td>3,651 (13.0)</td>
<td>3,553 (13.1)</td>
</tr>
<tr>
<td>Payer type, n (%)</td>
<td>Commercial</td>
<td>21,780 (59.0)</td>
<td>16,554 (59.0)</td>
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<td></td>
<td>Medicaid</td>
<td>958 (2.6)</td>
<td>730 (2.6)</td>
<td>708 (2.6)</td>
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<td></td>
<td>Medicare risk</td>
<td>2,591 (7.0)</td>
<td>1,976 (7.0)</td>
<td>1,910 (7.0)</td>
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<td>Self-insured</td>
<td>11,579 (31.4)</td>
<td>8,798 (31.4)</td>
<td>8,536 (31.4)</td>
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<td>Health plan type, n (%)</td>
<td>Health maintenance organization</td>
<td>7,205 (19.5)</td>
<td>5,490 (19.6)</td>
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<td>Point-of-service</td>
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<td>1,596 (5.7)</td>
<td>1,545 (5.7)</td>
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<td>Preferred provider organization</td>
<td>26,535 (71.9)</td>
<td>20,159 (71.8)</td>
<td>19,535 (71.8)</td>
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<td></td>
<td>Other/unknown</td>
<td>1,079 (2.9)</td>
<td>813 (2.9)</td>
<td>797 (2.9)</td>
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<td>Index year, n (%)</td>
<td>2016</td>
<td>14,009 (38.0)</td>
<td>10,654 (38.0)</td>
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<td></td>
<td>2017</td>
<td>12,178 (33.0)</td>
<td>9,249 (33.0)</td>
<td>8,984 (33.0)</td>
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<td></td>
<td>2018</td>
<td>10,722 (29.1)</td>
<td>8,154 (29.1)</td>
<td>7,894 (29.0)</td>
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<td>Charlson Comorbidity Index score, n (%)</td>
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<td>21,678 (58.7)</td>
<td>16,226 (57.8)</td>
<td>0.0446</td>
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<td>1</td>
<td>6,661 (18.0)</td>
<td>5,018 (17.9)</td>
<td>4,886 (18.0)</td>
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<td></td>
<td>2</td>
<td>4,128 (11.2)</td>
<td>3,172 (11.3)</td>
<td>3,071 (11.3)</td>
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<tr>
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<td>3</td>
<td>2,009 (5.4)</td>
<td>1,635 (5.8)</td>
<td>1,470 (5.4)</td>
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<td>≥4</td>
<td>2,433 (6.6)</td>
<td>2,007 (7.2)</td>
<td>1,839 (6.8)</td>
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<td>Mean (SD)</td>
<td>0.9 (1.5)</td>
<td>1.0 (1.6)</td>
<td>−0.0325</td>
<td>0.9 (1.5)</td>
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<tr>
<td>Median (IQR)</td>
<td>0 (1)</td>
<td>0 (1)</td>
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<td>0 (1)</td>
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<td>Diabetes Complication Severity Index, n (%)</td>
<td>0</td>
<td>18,318 (49.6)</td>
<td>13,884 (49.5)</td>
<td>0.0493</td>
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<td>1</td>
<td>7,810 (21.2)</td>
<td>5,950 (21.2)</td>
<td>5,775 (21.2)</td>
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<td>2</td>
<td>5,036 (13.6)</td>
<td>3,839 (13.7)</td>
<td>3,691 (13.6)</td>
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</table>
versus non-adherence cohorts (US$1,088 vs $1,204, p=0.01) (online supplemental figure 4).

Total mean all-cause medical costs were lower for the persistence and adherence cohorts compared with their reference groups (both p<0.0001). However, when basal insulin pharmacy costs were included, costs were not significantly different (persistence vs non-persistence, p=0.2; adherence vs non-adherence, p=0.3) (figure 1C–D). Full details of all-cause costs over year 1 are shown in online supplemental table 12.

### Healthcare resource utilization during year 2

For the subgroup analysis of HCRU and costs in the second year after initiating basal insulin therapy, we included patients with ≥2 years of continuous enrollment post-index. Of these patients, following IPTW adjustment, 19,205 and 14,084 were included in the persistence and non-persistence cohorts, respectively; 13,765 and 19,531 were included in the adherence and non-adherence cohorts, respectively. Many of the statistically significant differences in HCRU that were observed between cohorts in year 1 continued in year 2 (see figure 2A–B).

The proportion of patients with ≥1 all-cause hospitalization was significantly lower for persistence and adherence cohorts compared with their reference groups (persistence vs non-persistence, 11.5% vs 12.4%; adherence vs non-adherence, 11.3% vs 12.3%; both p<0.05). Similarly, the proportion with ≥1 all-cause ER visit was significantly lower for persistence and adherence cohorts compared with their reference groups (persistence vs non-persistence, 24.5% vs 26.2%; adherence vs non-adherence, 23.8% vs 26.1%; both p<0.001). Compared with their reference groups, persistence and adherence cohorts had higher all-cause utilization of outpatient services and laboratory tests (figure 2A–B). Full details of all-cause HCRU over year 2 are shown in online supplemental table 13.

### Healthcare costs during year 2

Total mean all-cause medical costs became similar between persistence and non-persistence cohorts (US$14,777 vs US$15,491, p=0.1303) but continued to be lower for adherence versus non-adherence cohorts (US$14,303 vs US$15,661, p=0.005). Total mean all-cause medical costs with basal insulin pharmacy costs became higher for persistence than for non-persistence cohorts (US$18,125 vs US$16,425, p=0.0003) but continued to be
similar between adherence and non-adherence cohorts (see figure 2C–D).

Over year 2 post-index, post-IPTW, total mean all-cause inpatient and ER costs continued to be lower for the persistence and adherence cohorts compared with their non-persistence and non-adherence reference groups, respectively. Total mean all-cause outpatient medical costs continued to be statistically similar between persistence versus non-persistence and adherence versus non-adherence cohorts. Full details of all-cause costs over year 2 are shown in online supplemental table 14.

Exploratory analyses of HbA1c changes

There was a greater reduction in HbA1c (from pre-index to post-index) for both the persistence versus non-persistence cohorts (−1.4% vs −1.1%, p=0.04) and the adherence versus non-adherence cohorts (−1.5% vs −1.1%, p=0.02). After controlling for age, sex, and baseline HbA1c, mean change in HbA1c was not significantly different between persistence and non-persistence cohorts. Adjusted mean change in HbA1c was greater for the adherence cohort than the non-adherence cohort (adherence, −1.4%; non-adherence, −1.2%; p=0.03).

Predictors of adherence and persistence

Prior antidiabetic medication use (both oral and injectable) was a significant predictor of persistence and adherence, respectively, among patients initiating basal insulin compared with those using only oral antidiabetic medication (see key results in figure 3 and full results in online supplemental table 15). Patients who were hospitalized or admitted to the ER during the pre-index period were less likely to have persistence and adherence with basal insulin therapy compared with those without a hospitalization or ER visit (both p<0.0001). Patients with at least one pre-index outpatient visit were more likely to have...
Epidemiology/Health services research

adherence and persistence with basal insulin therapy compared with those without ($p=0.03$ and $p=0.002$, respectively). Patients aged ≥35 years (multiple cohorts) were more likely to demonstrate persistence and adherence compared with patients aged 18–34 years (figure 3).

CONCLUSIONS
Main findings in context
In this retrospective study of US patients initiating basal insulin, we observed that non-persistence and non-adherence to basal insulin therapy were common and associated with significant healthcare utilization and cost implications. Patients who were persistent with, and adherent to, basal insulin had lower acute care HCRU (hospitalizations and ER visits) and all-cause direct medical costs in the one and 2-year follow-up periods when compared with respective non-persistence and non-adherence cohorts. However, patients demonstrating persistence and adherence had higher outpatient HCRU and higher pharmacy costs than patients demonstrating non-persistence and non-adherence, respectively.

Our findings suggest that greater persistence and adherence to basal insulin are associated with reduced acute HCRU and acute care costs in patients with type 2 diabetes. We found similar but smaller differences in acute care costs between adherence and non-adherence cohorts in the second year post-index (adherence vs non-adherence, US$5,383 vs US$6,390) as a similar analysis by Eby et al. (US$6,181 adherence vs US$10,054 non-adherence cohorts); however, that study also

Figure 2  Healthcare resource utilization by (A) persistence and (B) adherence in the second year following insulin initiation, post-IPTW adjustment. All-cause acute care and total medical healthcare costs by (C) persistence and (D) adherence in the second year following insulin initiation, post-IPTW adjustment. Total acute care costs include inpatient and ER costs. Total medical costs include inpatient, ER, and outpatient medical costs. ER, emergency room; IPTW, inverse probability of treatment weighting.
including patients on basal-bolus insulin. Perez-Nieves et al (2016) found that patients who continued basal insulin therapy in the first-year post-initiation had significantly lower medical costs compared with interrupters ($10,893 vs US$13,674) and discontinuers ($10,893 vs US$13,021).25 Additionally, Perez-Nieves et al. (2018) found that all-cause acute care costs were significantly lower for adherence cohorts than non-adherence cohorts in the 3 years post-index (US$22,112 vs US$25,458), but that study utilized a different claims database and included a different (3-year) follow-up period. The Perez-Nieves et al study (2018) did not use a distinct 1-year baseline period. Furthermore, both the Eby et al and Perez-Nieves et al studies used smaller populations and older data than we used in our study.

A systematic literature review of studies evaluating the impact of persistence and adherence to antidiabetic medications between 2010 and 2020 had findings that broadly correspond to our findings; overall rates of persistence and adherence were suboptimal while greater persistence and adherence was associated with clinical benefits.13 The systematic literature review also found that cost estimates varied greatly across studies, likely due to disparities in study variables and locations.13 Greater persistence and adherence were typically associated with higher pharmacy costs offset by lower hospitalization costs culminating in lower or budget-neutral total healthcare costs which is what we found in our year 2 results.13 Despite the wealth of studies cited in the aforementioned literature review, its authors still called for additional high-quality observational studies to enable systematic comparison of persistence and adherence across different drug classes.13 Our study adds a timely update to the literature and will hopefully encourage systematic comparisons across drug classes in the future.

Figure 3  Key predictors of (A) persistence with, and (B) adherence to, basal insulin therapy. ADM, antidiabetic medication; ER, emergency room; ref, reference cohort for OR calculations.
Adherence to basal insulin was also associated with better glycemic control in the 1-year post-initiation. Improved glycemic control could contribute to lower HCRU and associated medical costs. Persistence with basal insulin was also associated with reductions in HbA1c; however, after adjusting for confounding variables these differences were not significant. This could be explained by our more inclusive definition of persistence compared with our more stringent definition of adherence.

Although total direct medical costs were higher in the non-persistence and non-adherence cohorts than their respective comparator groups, basal insulin pharmacy costs were higher in the persistence and adherence cohorts and appear to offset the cost benefits conferred by their use. However, we must consider that this study focuses on the initial 1–2 years post-initiation of basal insulin and does not attempt to quantify external costs associated with non-persistence or non-adherence to basal insulin such as chronic diabetes complications, health-related quality of life, absenteeism, and time taken to visit medical facilities.

Of interest, patients with prior use of both oral and injectable antidiabetic medication had greater persistence and adherence to basal insulin compared with those with prior use of only oral antidiabetic medication. Experience with injectable treatment regimens may translate to enhanced adherence to the addition of insulin therapy. Greater adherence to antidiabetic medications has been associated with lower annual healthcare costs. It would be of interest to see if these findings translate to potential areas of intervention. One study found that behavior-based incentives improved patient adherence to diabetes testing regimens and decreased hospital admissions. Similarly, behavior-based methods should be considered to improve patient adherence to basal insulin therapy.

Patients with baseline hospitalization or ER visits were less likely to persist with or adhere to basal insulin therapy suggesting that the severity of their condition and/or corresponding treatment may be an impediment. The reverse could also be true; patient behaviors associated with persistence and adherence could lead to a higher risk of hospitalization. Another study also evaluated factors associated with likelihood of treatment interruption and discontinuation. As with our study, younger age, prior hospitalization, and prior ER visits were associated with higher odds of treatment interruption and discontinuation, while dyslipidemia and use of injectable antidiabetic medications were associated with lower odds of treatment interruption and discontinuation. A study of Medicare Part D enrollees with diabetes found that patients with higher comorbidity scores were less likely to adhere to their medications.

Strengths and limitations

The use of IPTW with stabilized weights to balance cohorts is a strength of this study. IPTW was used instead of propensity score matching because IPTW with stabilized weights preserves the sample size whereas propensity score matching discards some patients. The methodology we used to evaluate persistence and adherence to basal insulin is validated, robust, and data driven. The methodology accounts for drug delivery method which should more accurately account for usage in the real world.

This study identified statistically significant differences in HCRU and costs between groups demonstrating persistence compared with non-persistence and adherence compared with non-adherence. However, statistically significant differences are not necessarily indicative of economically significant differences.

This study used data from the PharMetrics Plus health insurance claims database. A claims database allows us to understand actual costs and have greater confidence about prescriptions filled, whereas electronic health records may show what a patient was prescribed but cannot guarantee what the patient received. The claims database used gave us a large sample size representative of the commercially insured US population below 65 years of age.

Due to temporal overlap, our year 1 analysis can only highlight the associations between persistence and adherence and HCRU and costs. However, our year 2 analysis suggests a causal relationship between persistence and adherence in the first year of basal insulin initiation and HCRU and costs in year 2. This study relies on administrative claims data collected for the purposes of payment. This data is not as detailed as medical records and there is a potential for miscoding or misclassification which could skew results. There was considerable overlap between patients included in persistence and adherence cohorts in this study which limits our ability to disentangle the impact of persistence compared with adherence. It is likely that factors which contribute to persistence also contribute to adherence.

The patient population included in this study differs in important ways from the wider US population and these differences limit our ability to generalize these results accordingly. The PharMetrics Plus database is limited to patients with commercially managed insurance, thus these findings may not be representative of uninsured patients or patients with traditional Medicare or Medicaid.

Our findings could be influenced by healthy user bias. The patients who were most persistent and adherent in this study are likely to have better health behaviors overall which could influence their healthcare costs and utilization independently of persistence and adherence. Patients included in this study were required to have continuous enrollment to provide an adequate clinical history. Excluding patients who disenrolled or died during the course of the study may bias this study towards a healthier subset of patients. We attempted to control for confounding variables with IPTW, but unmeasured confounders could continue to introduce bias. We did not control for socioeconomic status, ethnicity, or duration of diabetes due to the limited availability or unavailability of this data in the databases used. Our exploratory
analysis included a subset of patients with HbA1c values available at multiple times of interest, potentially indicating that these patients are being more actively managed than other patients with type 2 diabetes. Compared with the overall cohort, relatively few patients had HbA1c measurements available; therefore, these findings could be strongly biased.

This study focuses on patients managing type 2 diabetes with basal insulin pre-COVID-19 which helps to understand the effect of persistence and adherence on HCRU and direct medical costs before the massive temporary disruption caused by COVID-19. However, some of the impacts COVID-19 has had on healthcare may be permanent rather than temporary. Future studies will need to investigate the impact of persistence and adherence to basal insulin on HCRU and direct medical costs in a post-COVID-19 world.

In conclusion, we found that greater persistence and adherence to basal insulin therapy is associated with lower HCRU, particularly utilization of acute care, and direct medical costs. Further research and clinical efforts to improve persistence and adherence to basal insulin therapy may significantly impact the healthcare burden of type 2 diabetes.

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NN, KKM, TN, JR, and VD contributed to the design of the study. JM and VD conducted the statistical analyses with non-author assistance from YW (acknowledged above). All authors participated in interpretation of the data and drafting and revision of the manuscript. All authors reviewed and approved the final, submitted version. VRA is the guarantor of the manuscript and takes responsibility for the data and the accuracy of the data analysis.

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**Competing interests**
NN, KKM, and JR are employees and shareholders of Novo Nordisk. TN is a research fellow with Novo Nordisk and Rutgers University. VD and JM are employees of IQVIA and received funding from Novo Nordisk for the current study. VRA is a consultant for Applied Therapeutics, Fractyl Healthy, Pfizer, Novo Nordisk, Sanofi and her institution has received research grants/contracts from Applied Therapeutics, Eli Lilly, Fractyl Health, Pfizer, Novo Nordisk, Sanofi. Her spouse is an employee of Janssen Pharmaceuticals.

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**Data availability statement**
Data are available upon reasonable request. The underlying data sets used in this study are available with permission from IQVIA, but restrictions apply to the availability of these data, which were used under license for the current study and therefore are not publicly available.

**Supplemental material**
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