



**Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study**

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**Title:**

Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study

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## Article Summary

### Article Focus

- Do differences seen in the outcomes of randomized controlled trials comparing insulin glargine and neutral protamine Hagedorn (NPH) translate to improved real-world outcomes in employed adults living in the United States?

### Key Messages

- Insulin glargine was associated with better persistence, lower inpatient admission, which offsets its higher drug cost, and lower indirect costs from short-term disability, than NPH insulin
- Reduced short-term disability and improved adherence with insulin glargine may improve long-term productivity, compared with NPH insulin, and provide benefits to both employees and their employers

### Strengths and Limitations

- *Strengths*
  - The MarketScan database represents a large and diverse data source.
  - The database captures detailed information on healthcare resource utilization and productivity, as measured by short-term-disability.
  - The use of propensity-score-matching methodology minimizes the selection bias due to observed differences between insulin glargine and NPH groups.
- *Limitations:*
  - As with all retrospective studies, causality of treatment effects cannot be established in this study.
  - Despite its size and diversity, it should not be assumed that the sample obtained is representative of the overall US population.
  - It is unlikely that rates of hypoglycemia and other clinical outcomes would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia, could be assessed.

**[Abstract]****Limit: 300 words****Current: 285 words**

**Objectives:** To compare real-world effectiveness of initiating insulin glargine (GLA) versus neutral protamine Hagedorn (NPH) insulin among employees with type 2 diabetes mellitus (T2DM).

**Design:** Retrospective cohort study

**Setting:** MarketScan Commercial Claims and Encounters/Health and Productivity Management Databases 2003–2009.

**Participants:** A total of 534 patients were matched and analyzed (GLA: 356; NPH 178) with no significant differences in baseline characteristics. Adult employees with T2DM who were previously treated with oral antidiabetic drugs and/or glucagon-like peptide 1 receptor agonists, and initiated insulin with GLA or NPH. Patients were included if they were continuously enrolled in healthcare and short-term-disability coverages for 3 months before (baseline) and 1 year after (follow-up) initiation. Selection bias was addressed by 2:1 propensity score matching (PSM).

**Primary and secondary outcome measures:** Persistence and adherence to insulin were calculated and compared. Clinical outcomes were hypoglycemia and daily average consumption of insulin. Total and diabetes-specific healthcare resource utilization and costs were compared. Loss in productivity, as measured by short-term disability, and the associated costs, were compared.

**Results:** GLA patients were more persistent and adherent (both  $P < 0.05$ ), with lower rates of hospitalization (23.0% vs 31.4%;  $P = 0.036$ ) and endocrinologist visits (19.1% vs 26.9%;  $P = 0.038$ ), similar hypoglycemia rates (both 4.4%;  $P = 1.0$ ), higher diabetes drug costs (\$2,031 vs \$1,522;  $P < 0.001$ ), but similar total healthcare costs (\$14,550 vs \$16,093;  $P = 0.448$ ) and total diabetes-related healthcare costs (\$4,686 vs \$5,604;  $P = 0.416$ ). Short-term disability days and costs were marginally lower in the GLA cohort (16.0 vs 24.5 days;  $P = 0.086$  and \$2,824 vs \$4,363;  $P = 0.081$ , respectively).

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3 **Conclusion:** Employees with T2DM initiating GLA instead of NPH were more persistent and  
4 adherent with their treatment. Their higher drug cost was offset by lower medical costs.  
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6 Marginally lower short-term-disability costs were incurred among GLA patients.  
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## 10 INTRODUCTION

11 In the United States (US), diabetes affects an estimated 25.8 million people (8.3% of the US  
12 population).[1] Type 2 diabetes mellitus (T2DM) accounts for substantial clinical sequelae,  
13 including microvascular and macrovascular complications,[1] and leads to significant direct  
14 and indirect costs associated with treatment and lost productivity. Furthermore, T2DM  
15 imposes an important economic burden to self-insured employers.[2] People with diabetes  
16 incur more medical costs, have more frequent physician encounters and use more medical  
17 services than people without diabetes.[3] In 2007, approximately 1 in 5 healthcare dollars in  
18 the US was spent caring for people with diabetes, and T2DM in the US incurred costs  
19 estimated at \$174 billion.[4] Of this total, direct medical costs comprised an estimated \$116  
20 billion, while indirect costs – including treating the consequences of inadequate glycemic  
21 control and other complications of diabetes – were estimated at \$58 billion.[4]  
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30 Diabetes-related costs to employees and employers are associated with disability and  
31 reduced productivity, work loss, and associated comorbidities.[5, 6] In one survey, the  
32 impact of diabetes-associated disability in the US, in terms of aggregate losses, was  
33 estimated at \$9.3 billion in a single year (1994).[7] Similarly, a longitudinal cohort study  
34 reported estimated costs to employers and employees in lost productivity in the US of \$7.3  
35 billion annually, and \$58.6 billion in total over an 8-year period (1992–2000). This figure  
36 included \$31.7 billion due to disability, \$4.4 billion in lost income due to early retirement, \$0.5  
37 billion due to sick days, and \$22 billion due to premature mortality.[8] In addition, the micro-  
38 and macrovascular complications associated with diabetes contribute further to the overall  
39 costs and productivity reductions. Macrovascular comorbidities are associated with  
40 additional costs of \$5,120, 13.03 missed workdays, and 7.60 bed days per patient, and the  
41 marginal lost productivity cost has been estimated at \$2,388 annually per patient.[9] With  
42 regard to microvascular complications, diabetic retinopathy resulted in significantly higher  
43 costs for affected employees (annual direct and indirect costs of \$18,218 and \$3,548,  
44 respectively), compared with employees with diabetes but no retinopathy (\$11,898 and  
45 \$2,374).[10] In addition, for specific populations at high risk of diabetes, the condition  
46 predicts absenteeism among obese and morbidly obese workers.[11] Overall, reduced  
47 national productivity related to diabetes accounted for \$58 billion in 2007 in the US.[4]  
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3 A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides  
4 clinically relevant improvements in glycemic control with a good safety profile.[12] In  
5 addition, early improvements in glucose control can reduce the long-term risk of  
6 macrovascular events associated with T2DM, as well as reduce microvascular  
7 complications.[13] Options for basal insulin include insulin glargine, a once-daily, long-acting  
8 basal insulin analog, or Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting  
9 insulin, typically administered once or twice daily. Clinical studies have shown that the  
10 efficacy of these two agents is similar, but that there is a lower risk of hypoglycemia,  
11 particularly nocturnal hypoglycemia, with insulin glargine.[14-16] Notably, hypoglycemia  
12 contributes considerably to the costs of diabetes. In a recent study of 2,664 employees, the  
13 annualized cost of hypoglycemia was \$3,241; moreover, patients with hypoglycemia  
14 experienced 77% more short-term disability annually than those without.[17]

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23 Simplicity of treatment regimen is important for those transitioning from oral to insulin  
24 therapy. The once-daily regimen provided by insulin glargine may also have implications for  
25 increased patient persistence and adherence[18] and, consequently, may improve  
26 outcomes. In general, treatment complexity for chronic conditions – including, though not  
27 limited to the need to administer more than one injection daily – correlates with poor  
28 adherence.[19] Reasons given for diabetes patients missing insulin doses include: needing  
29 more daily injections, injections interfering with daily activities, and embarrassment.[20] Such  
30 considerations, in relation to convenience and adherence, may be particularly important for  
31 working people who have T2DM. In reality, patients taking insulin glargine have been shown  
32 to be more likely to persist with their medication than those taking NPH insulin.[21]

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40 Successful treatment, including adherence to medication, is key to the improvement of  
41 outcomes for employees. Better adherence to diabetes medication is associated with  
42 improved glycemic control and decreased healthcare resource utilization.[22] In addition,  
43 because adherence to medication reduces the incidence of complications, it is associated  
44 with improved work-related outcomes, such as reducing the number of short-term disability  
45 days.[23] Moreover, although adherence is associated with higher drug costs, overall  
46 healthcare costs decrease in adherent patients with diabetes and other chronic  
47 conditions.[24-25] People with untreated diabetes, or those with a long duration of the  
48 disease, are at increased risk of occupational injury, which is minimized in treated patients  
49 who are adherent to medication.[26] Effective pharmacological management of diabetes with  
50 adequate compliance also results in substantial cost benefits to employers.[24,27]

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3 Although there are data in support of the clinical benefits of basal insulins there is currently a  
4 paucity of real-world information about the impact of different basal insulin regimens on  
5 healthcare utilization and employee disability, including their associated costs. This analysis  
6 was conducted in order to assess persistence with and adherence to medication, healthcare  
7 resource utilization and employees' loss-in-productivity, as measured by short-term-  
8 disability, and associated costs among employees with T2DM treated with insulin glargine or  
9 NPH insulin in the real-world setting.  
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## 14 **METHODS**

### 15 **Database**

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17 This study is a retrospective analysis of patients' medical records extracted from the  
18 MarketScan Commercial Claims and Encounters Database 2003–2009. This database  
19 captures person-specific clinical utilization, expenditures, and enrolment across inpatient,  
20 outpatient, prescription drug, and carve-out services from about 100 large employers, health  
21 plans, and government and public organizations. Short-term disability data were extracted  
22 from the MarketScan Health and Productivity Management Database, which is an integrated  
23 database that contains information on absence, short-term disability, and workers'  
24 compensation experience. This information is linkable to the medical, pharmacy, and  
25 enrolment data in the MarketScan Commercial Claims and Encounters Database for these  
26 employees, providing a unique and valuable resource for examining health and productivity  
27 issues for an employed, privately insured population.  
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### 36 **Cohort selection criteria**

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38 Included in the analysis were employees of 18 years of age or older with T2DM, defined as  
39 having made at least one inpatient visit or two physician visits dated at least 30 days apart,  
40 with a primary or secondary diagnosis of diabetes mellitus type II or unspecified type not  
41 stated as uncontrolled (International Classification of Diseases, 9th Revision, Clinical  
42 Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or unspecified type  
43 uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine or NPH insulin  
44 with the date of the first such claim being the index date; enrolled for medical and pharmacy  
45 healthcare benefits and work benefits for short-term disability for 3 months prior to insulin  
46 initiation (baseline period), and 12 months after insulin initiation (follow-up period); and on at  
47 least one oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline  
48 period. The patient cohorts for comparison were determined on the basis of use of insulin  
49 glargine or NPH insulin at initiation of insulin therapy. Outcomes were compared between  
50 the matched cohorts after 1 year of follow-up.  
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### Baseline characteristics

Records were analyzed to assess baseline characteristics, including: gender; age; OAD use; comorbidities; healthcare utilization/costs; and short-term disability. Follow-up records were analyzed to assess treatment persistence, adherence, hypoglycemic events, healthcare resource utilization, cost, and short-term disability after initiation of insulin therapy.

#### Persistence and Adherence

Measuring persistence with insulin treatment is challenging due to its non-fixed dose schedule. Consistent with an existing published study,[28] persistence was measured here as the time the patient had remained on study drugs without discontinuation or switching following insulin initiation. Study medication was considered discontinued if the prescription was not refilled within the expected time of medication coverage, defined as the 90th percentile of the time, stratified by the metric quantity supplied, between the first and second fills among patients with at least one refill. Patients who restarted their initial medication after discontinuation, as defined above, were also considered non-persistent patients. Sensitivity analyses were also conducted using the 75th and 95th percentiles of the time.

Treatment adherence was measured during the 1-year follow-up by both the traditional medication possession ratio (MPR) and the adjusted MPR, which allows for differences in insulin-device package size [29] (insulin glargine, for example, is packaged either in 10 mL vials with a total of 1,000 units, or in a 3 mL disposable device in a package of 5 pens with a total of 1,500 units). The adjusted MPR was calculated by multiplying the traditional MPR (the total days' supply of all filled study drug prescriptions in the analysis period divided by the number of days in the analysis period) by the average number of days between prescription refills for patients using insulin divided by the average days' supply for patients using insulin.

#### Clinical outcomes

Clinical outcomes such as hypoglycemia and daily average consumption (DACON) of insulin were examined. Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia (ICD-9 code 250.8–diabetes with other specified manifestations; 251.0–hypoglycemic coma; 251.1–other specified hypoglycemia; or 251.2–hypoglycemia, unspecified).[30] A1C data were not available in this study.

#### Healthcare resource utilization and cost



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3 Categories of healthcare resource utilization included numbers of outpatient visits,  
4 emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total  
5 outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare  
6 resource utilization included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx),  
7 and use of anti-hyperglycemic medications, glucose meters and supplies.  
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12 Healthcare costs were computed as paid amounts of adjudicated claims, including insurer  
13 and health-plan payments, copayments and deductibles. Diabetes-specific healthcare costs  
14 included those related to a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx).  
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18 **Loss in productivity and its associated costs**

19 Loss in productivity was measured by the total number of days patients were on short-term  
20 disability during the baseline and follow-up periods. The associated costs for short-term  
21 disability were calculated as 70% of \$240 (a figure reflecting the average daily wage paid to  
22 employees of large employers),[31] which amounts to \$168, since disability programs  
23 typically pay for 70% of lost income.[32]  
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29 **Total cost**

30 Total cost was assessed by combining direct costs (healthcare) and indirect costs (short-  
31 term disability costs), and comparisons between groups were made.  
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35 Costs were adjusted for inflation to 2010 US dollars using the medical care component of the  
36 Consumer Price Index.  
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### 39 **Statistical analyses**

40 To remove the observed baseline selection bias between the two study cohorts, propensity  
41 score matching (PSM) methodology[33] was implemented, with a stringent 2:1 matching of  
42 patients initiating insulin glargine or NPH insulin. Propensity scores for initiating insulin  
43 glargine vs NPH were calculated from a logistic regression model that estimated the  
44 likelihood of initiating insulin glargine based on the observed patient characteristics.  
45 Covariates were selected based on their hypothesized confounding relationship with the  
46 outcome variables, and included age, gender, region, health plan type Charlson Comorbidity  
47 Index, and baseline concomitant medications, hypoglycemic events, healthcare utilization  
48 (overall or disease-related), co-pays, and healthcare cost (overall or disease-related).  
49 Sensitivity analyses were also conducted using 1:1 and 3:1 PSM.  
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Among the matched cohorts, all study variables, including baseline and outcome measures, were analyzed descriptively. Results were stratified by treatment cohort. For dichotomous variables, p values were calculated according to the Mann–Whitney U test; for continuous variables, t tests were used to calculate p values.

Kaplan–Meier survival curve and the log-rank test were used to compare 1-year treatment persistence. The relationship between hospitalization and short-term disability was investigated by chi-squared test and Pearson's correlation analysis.

## RESULTS

### Baseline characteristics

Data from 2,454 patient records were eligible for the 1-year follow-up analyses: 2,250 in the insulin glargine (GLA) cohort, and 204 in the NPH insulin (NPH) cohort. The 2:1 PSM yielded a total of 534 patients (GLA: 356; NPH 178). At baseline, the two patient cohorts were well matched (table 1). Overall, 43.8% of the patients included in the analysis were women; mean age was 49 years (range: 20–64 years), and the mean number of OADs was 1.8. The baseline hospitalization rate was 15.2%, with a mean short-term disability of 3.0 days.

**Table 1.** Baseline characteristics

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
<b>Gender, female (%)</b>	153 (42.9%)	81 (45.5%)	0.5789
<b>Age, years, mean ± SD</b>	49 ± 10	49 ± 10	0.7580
<b>Health plan, n (%)</b>			0.9390
	CDHP	2 (1.1%)	
	Comprehensive	18 (10.1%)	
	HMO	36 (20.2%)	
	POS	29 (16.2%)	
	PPO	93 (52.2%)	
<b>Pen use, n (%)</b>	59 (16.5%)	33 (18.5%)	
<b>Antidiabetic drugs, n (%)</b>			
	Metformin	132 (74.1%)	0.8893
	Sulfonylureas	105 (58.9%)	0.4138
	Thiazolidinediones	68 (38.2%)	0.8497
	DPP-4 inhibitors	6 (3.3%)	0.5785
	Exenatide	11 (6.1%)	0.3579
<b>Number of OADs, mean ± SD</b>	1.81 ± 0.73	1.80 ± 0.75	0.9015
<b>Charlson Comorbidity Index, mean ± SD</b>	0.284 ± 0.819	0.281 ± 1.159	0.9770
<b>Comorbidities, n (%)</b>			
	Obesity	4 (2.2)	0.4758
	Hypertension	39 (21.9)	0.8817
	Hyperlipidemia	22 (12.3)	0.6305
	Congestive heart failure	4 (2.2)	0.4728
	Retinopathy	5 (2.8)	0.5357
	Neuropathy	8 (4.4)	0.6752
	Nephropathy	3 (1.6)	0.1270
<b>Total healthcare utilization, n (%) or mean ± SD</b>			
	Hospitalizations	28 (15.7%)	0.7980
	Total hospitalization days	0.72 ± 2.11	0.3018
	ER visits	38 (21.3%)	0.7680
	Endocrinologist visits	25 (14.0%)	0.2550

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Hospitalization/patient	0.16 ± 0.39	0.17 ± 0.42	0.6458
ER visits/patient	0.31 ± 0.67	0.28 ± 0.68	0.6817
Endocrinologist visits/patient	0.15 ± 0.48	0.19 ± 0.55	0.3844
<b>Diabetes-related healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	34 (9.5%)	20 (11.2%)	0.5426
ER visits	37 (10.3%)	17 (9.5%)	0.7608
Endocrinologist visits	36 (10.1%)	23 (12.9%)	0.3290
Office visits	297 (83.4%)	138 (77.5%)	0.0982
Hospitalizations/patient	0.10 ± 0.29	0.11 ± 0.32	0.5434
ER visits/patient	0.13 ± 0.40	0.11 ± 0.34	0.5570
Endocrinologist visits/patient	0.14 ± 0.47	0.17 ± 0.53	0.4951
Office visits/patient	1.74 ± 1.43	1.60 ± 1.44	0.2782
Total hospitalization days	0.52 ± 2.31	0.41 ± 1.49	0.4975
<b>Any hypoglycemia visit, n (%)</b>	15 (4.2%)	6 (3.4%)	0.9197
<b>Total healthcare cost, mean ± SD</b>			
Inpatient cost	2756 ± 12393	1958 ± 8241	0.3766
Outpatient cost	1385 ± 3652	1766 ± 4243	0.3068
ER cost	181 ± 476	144 ± 515	0.4138
Prescription cost	937 ± 1236	926 ± 1065	0.9117
Total cost	5259 ± 14237	4794 ± 10731	0.6735
<b>Total diabetes-related healthcare cost, mean ± SD</b>			
Inpatient cost	1304 ± 6588	811 ± 3447	0.2570
Outpatient cost	242 ± 321	274 ± 505	0.4393
ER cost	46 ± 216	34 ± 195	0.5346
Prescription cost	294 ± 293	285 ± 309	0.7474
Supply cost	48 ± 97	46 ± 92	0.7766
Total cost	1934 ± 6551	1450 ± 3485	0.2658
<b>Co-pay, n (%)</b>			0.8694
\$0–\$15	166 (46.6%)	87 (48.8%)	
\$15–\$30	147 (41.2%)	71 (39.8%)	
\$30+	42 (11.7%)	20 (11.2%)	
Unknown	1 (0.2%)	0 (0.0%)	
<b>Short-term disability, mean ± SD</b>			
Occurrence count	0.12 ± 0.34	0.12 ± 0.37	0.9310
Days	3.10 ± 12.97	2.98 ± 12.9	0.9153
Cost	538 ± 2250	534 ± 2349	0.9856
<b>Total cost (healthcare + short-term disability), mean ± SD</b>	5797 ± 15005	5328 ± 12174	0.6987

CDHP, consumer-driven health plan; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; ER, Emergency Room; HMO, health maintenance organization; NPH, neutral protamine Hagedorn insulin; OADs, oral antidiabetic drugs; POS point of service; PPO, preferred provider organization; SD, standard deviation.

### Persistence and adherence

During the 1-year follow-up, patients receiving insulin glargine were significantly more persistent (table 2, figure 1) and adherent compared with those in the NPH insulin cohort (table 2). Over half (54.5%) of patients on insulin glargine were persistent, compared with 43.8% of those on NPH (P=0.0225); Patients stayed on insulin glargine treatment for a significantly longer period (approximately 22 days longer) than those on NPH insulin (284 vs 262 days, P=0.0178). The Kaplan–Meier survival curve shows that patients treated with NPH discontinued sooner than those treated with insulin glargine (log-rank test P-value=0.0073; figure 2). Sensitivity analyses using the 75th and 95th percentiles yielded similar results, with all indicating better persistence with insulin glargine compared with NPH

insulin (75th percentile: 34.0% vs 28.1%, P=0.17; 95th percentile: 67.2% vs. 57.9%, P=0.039, respectively). Both traditional and adjusted MPR values indicated a significantly better adherence to treatment with insulin glargine, compared with NPH insulin (table 2, figure 1).

**Table 2. Follow-up treatment persistence, hypoglycemia, healthcare utilization and loss in productivity**

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
<b>Persistence/adherence, n (%) or mean ± SD</b>			
Treatment persistence	186 (54.5)	75 (43.8)	0.0225
Treatment persistence days	283.85 ± 96.92	261.77 ± 103.35	0.0178
MPR,	0.50 ± 0.28	0.45 ± 0.30	0.0418
Adjusted MPR	0.67 ± 0.33	0.61 ± 0.35	0.0380
DACON	30.6 ± 21.1	35.8 ± 31.9	0.0740
<b>Hypoglycemia, n (%) or mean ± SD</b>			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
<b>Total healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	82 (23%)	56 (31.4%)	0.0360
ER visits	104 (29.2%)	57 (32.0%)	0.5049
Endocrinologist visits	68 (19.1%)	48 (26.9%)	0.0377
Office visits	352 (98.8%)	177 (99.4%)	0.5251
Hospitalizations/patient	0.28 ± 0.58	0.41 ± 0.73	0.0353
ER visits/patient	0.56 ± 1.43	0.54 ± 1.03	0.8353
Endocrinologist visits/patient	0.61 ± 1.57	0.94 ± 1.84	0.0422
Office visits/patient	18.37 ± 17.43	18.30 ± 14.98	0.9615
Total hospitalization days	1.29 ± 4.54	2.06 ± 4.98	0.0754
<b>Diabetes-related healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	45 (12.6%)	27 (15.1%)	0.4201
ER visits	43 (12.0%)	27 (15.1%)	0.3186
Endocrinologist visits	68 (19.1%)	45 (25.2%)	0.0993
Office visits	341 (95.7%)	168 (94.3%)	0.4689
Hospitalizations/patient	0.14 ± 0.38	0.15 ± 0.36	0.6801
ER visits/patient	0.20 ± 0.81	0.16 ± 0.40	0.5207
Endocrinologist visits/patient	0.56 ± 1.45	0.80 ± 1.65	0.1100
Office visits/patient	5.69 ± 3.98	5.56 ± 4.23	0.7293
Total hospitalization days	0.56 ± 2.50	0.53 ± 1.99	0.8659
<b>Loss in productivity, mean ± SD</b>			
Short-term disability occurrences	0.36 ± 0.70	0.38 (0.70)	0.7944
Short-term disability days	15.96 ± 38.78	24.51 ± 60.33	0.0862

DACON, daily average consumption; ER, Emergency Room; NPH, neutral protamine Hagedorn insulin; SD, standard deviation

### Clinical outcomes

Clinical outcomes of the two agents were similar, both in terms of hypoglycemia-related event rates (both cohorts had overall hypoglycemia rates of 4.4%; P=1.0) and DACON (GLA: 30.6 units vs NPH: 35.8 units, P=0.074) (table 2).

### Healthcare utilization and cost

In terms of healthcare utilization and cost, patients in the insulin glargine cohort also had lower rates of hospitalization, compared with those in the NPH insulin cohort (23.0% vs 31.4%; P=0.036, respectively; table 2), and of endocrinologist visits (19.1% vs 26.9%;

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3 P=0.038), despite similar utilization at baseline (table 2). With respect to cost outcomes, the  
4 total overall healthcare costs were similar for the insulin glargine and NPH insulin cohorts  
5 (\$14,550vs \$16,093, respectively; P=0.448), as were total diabetes-related healthcare costs  
6 (\$4,686vs \$5,604; P=0.416) (figure 3). Similar total diabetes-related healthcare costs were  
7 reported despite significantly higher diabetes-related prescription costs for the insulin  
8 glargine cohort (\$2,031), compared with the NPH insulin cohort (\$1,522).  
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### 13 **Loss in productivity and its associated costs**

14 In terms of loss in productivity and the associated costs for employers, the incidence of  
15 claims for short-term disability was 0.36 per patient per year in the insulin glargine group,  
16 compared with 0.38 in the NPH insulin group (P=0.7944). However, the total number of  
17 short-term disability days and the associated cost were marginally lower in the insulin  
18 glargine group (16.0 vs 24.5 days; P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively.  
19 figure 3).  
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26 In terms of combined total costs, a non-significant difference in favor of insulin glargine  
27 patients was evident (\$17,374for GLA vs \$20,455for NPH, P=0.204).  
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### 30 **Correlations**

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32 The chi-squared test comparing any hospitalization and any occurrence of short-term-  
33 disability in the 1:2 matched cohorts showed that patients with hospitalizations were  
34 significantly more likely to have at least one claim for short-term disability (60.1% vs 15.7%,  
35  $e<0.001$ , data not shown). Pearson's correlation test in the 1:2 matched cohorts showed that  
36 the number of hospitalizations was highly correlated with the number of short-term disability  
37 claims ( $r = 0.40$ ,  $P<0.0001$ ), as was the number of hospitalization days with the number of  
38 short-term-disability days ( $r = 0.33$ ,  $P<0.0001$ ).  
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### 44 **Sensitivity analysis**

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46 The sensitivity analyses using 1:1 and 3:1 PSM yielded similar results overall. In the 1:1  
47 PSM analysis (n=199, both cohorts), persistence with treatment was higher with insulin  
48 glargine than with NPH insulin (75th percentile: 32.8% vs 26.0%, P=0.146; 90th percentile:  
49 51.0% vs 41.1%, P=0.052; 95th percentile: 66.1% vs 54.6%, P=0.022). Treatment adherence  
50 was also higher with insulin glargine than with NPH insulin (MPR: 0.49 vs 0.43, P=0.039;  
51 adjusted MPR: 0.66 vs 0.60; P=0.070). A significantly lower hospitalization rate (26.1% vs  
52 36.1%, P=0.030), lower endocrinologist visit rate (17.0% vs 26.1%, P=0.028), fewer  
53 hospitalization days (1.32 vs 2.29 days, P=0.026), fewer short-term disability days and lower  
54 associated costs (12.33 days vs 27.67 days; P=0.002 and \$2,173vs \$4,942; P=0.002,  
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3 respectively) were reported with insulin glargine than with NPH insulin in the 1:1 PSM  
4 analysis. Total costs in the 1:1 matched cohort were also significantly lower in the GLA  
5 cohort than in the NPH cohort (\$15,720 vs \$21,398,  $P=0.022$ ). The results from the 3:1 PSM  
6 analysis ( $n=480$ , GLA,  $n=160$ , NPH) were consistent with those from the 2:1 PSM analysis.  
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## 10 **DISCUSSION**

11 In this real-world study, use of insulin glargine was associated with better persistence and  
12 adherence than NPH insulin. In addition, a lower healthcare resource utilization was  
13 associated with insulin glargine than NPH insulin, in terms of hospitalizations and  
14 endocrinologist visits, over 1 year of follow-up. Rates of hypoglycemia-related events were  
15 similar with the two treatments. Furthermore, diabetes drug-related costs were higher with  
16 insulin glargine than with NPH insulin, likely due to higher drug price of insulin glargine, and  
17 also the improved persistence/adherence associated with it. However, both total diabetes-  
18 related and total healthcare costs were similar in the two groups, as a consequence of the  
19 fewer hospitalizations and lower inpatient costs associated with the use of insulin glargine,  
20 compared with NPH insulin. In regard to short-term disability in both primary and sensitivity  
21 analyses, marginally fewer short-term disability days and lower associated costs were  
22 reported in the insulin glargine cohort than in the NPH insulin cohort. It is likely that the  
23 reduction of short-term disability are related to fewer hospitalizations in the insulin glargine  
24 cohort. Indeed, the correlation analysis showed that patients with any hospitalizations were  
25 significantly more likely to claim for short-term disability: both the number and duration of  
26 hospitalizations were highly correlated with the number of claims and the duration of short-  
27 term disability.  
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39 A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in  
40 patients with T2DM have indicated that insulin glargine represents a cost-effective treatment  
41 option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at  
42 least as effective glycemic control as NPH insulin, and to be cost effective in a range of  
43 countries and settings.[34-40]  
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47 Basal insulin analogs, such as insulin glargine, have been shown to have several  
48 advantages compared to NPH insulin including less pharmacologic variability, lower risk of  
49 hypoglycemia, and greater impact on quality of life.[41] The increased adherence associated  
50 with insulin glargine, as shown in this study, may lead to better clinical outcomes and  
51 potentially improve work-related outcomes.[22, 23, 26] Diabetes-related disability has been  
52 shown to result in loss of work place productivity;[42-46] In this study, we observed fewer  
53 short-term disability days in patients on insulin glargine, compared with those on NPH  
54 insulin, although the difference was not statistically significant in all analysis. This finding  
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3 suggests that initiation of therapy with insulin glargine may help increase workplace  
4 productivity among employed patients with T2DM.  
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8 As with all retrospective studies, issues of sampling bias should be taken into account when  
9 interpreting these results. However, the use of PSM methodology in this study should reduce  
10 the impact of any such bias. Causality of treatment effects cannot be established in this  
11 study. Although the MarketScan Database represents a large diverse data source, it should  
12 not be assumed that the sample obtained is representative of the overall US population.  
13 Furthermore, the similar rate of hypoglycemia is inconsistent with existing literature, as  
14 previous evidence suggests a lower risk of hypoglycemia with insulin glargine, compared  
15 with NPH insulin in previous studies.[14, 34] It is unlikely that rates of hypoglycemia would  
16 be captured with the same level of sensitivity in this retrospective analysis as they would in a  
17 randomized clinical trial. Further, the low overall hypoglycemia rate in both cohorts, may  
18 have resulted in insufficient statistical power to detect significant differences. Coding issues  
19 in the claim data may also have contributed to the lack of statistical robustness. Finally, A1C  
20 data were not available, so neither the effectiveness of glycemic control nor the association  
21 with hypoglycemia, could be assessed.  
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### 30 **CONCLUSION**

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32 This study showed reduced healthcare utilization in employees with T2DM initiating insulin  
33 glargine, which together with potential reductions in periods of short-term disability, may lead  
34 to increased workplace productivity. Furthermore, use of insulin glargine resulted in better  
35 persistence and adherence, compared with NPH insulin at similar total healthcare costs,  
36 despite higher drug-related costs. Better persistence and adherence may lead to long-term  
37 health benefits. In summary, insulin glargine represents a cost-effective treatment option,  
38 compared with NPH insulin, and may offer additional benefits to patients with T2DM and  
39 their employers. Due to the retrospective nature of this study, however, further studies need  
40 to be conducted to confirm these findings.  
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48  
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### 53 **DISCLOSURES**

54  
55 LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis  
56 U.S.  
57

58 RM and WW: Employees of sanofi-aventis U.S.  
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**CONTRIBUTIONS**

LW: Active in study design, statistical plan, data analysis, drafting, and review of manuscript.

WW: Active in creating the concept and study design, drafting, and review of manuscript.

RM: Active in creating the concept and study design, drafting, and review of manuscript.

LX: Role in statistical analysis and review of manuscript.

OB: Active in creating the study design, statistical plan, and review of manuscript.

**DATA SHARING**

Additional data is available by e-mailing Dr Onur Baserobaser@statinmed.com

**COMPETING INTERESTS**

LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis U.S. RM and WW: Employees of sanofi-aventis U.S.

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3 **Figure legends**

4 **Figure 1** Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

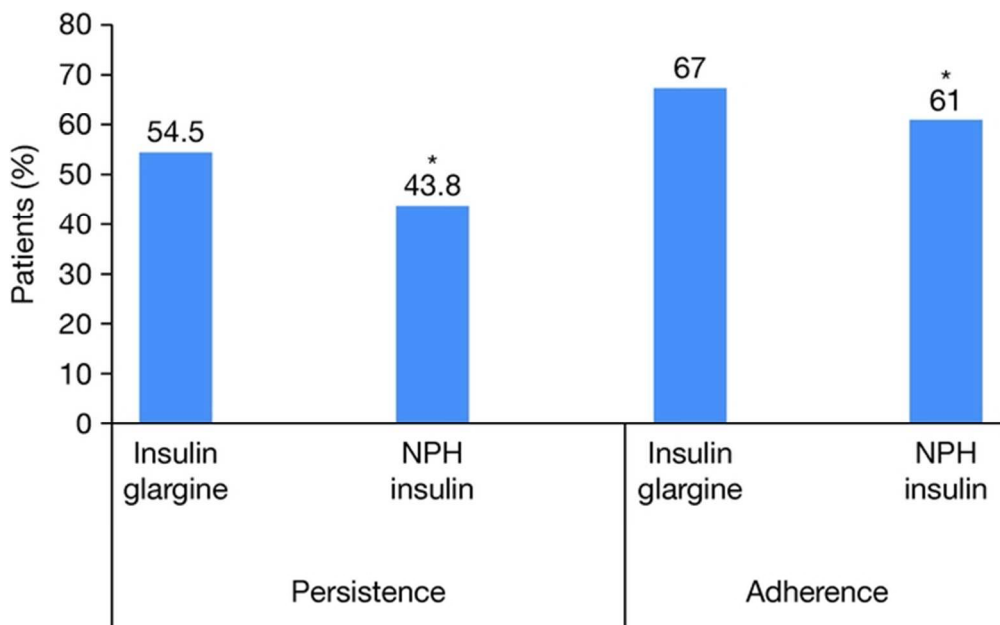
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7 \*P<0.05 vs insulin glargine

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11 **Figure 2** Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine  
12 and NPH insulin

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17 **Figure 3** 1-year short-term disability and direct healthcare costs. (Total between-group  
18 differences did not reach statistical significance).

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21 \*P<0.0001 vs insulin glargine

For peer review only



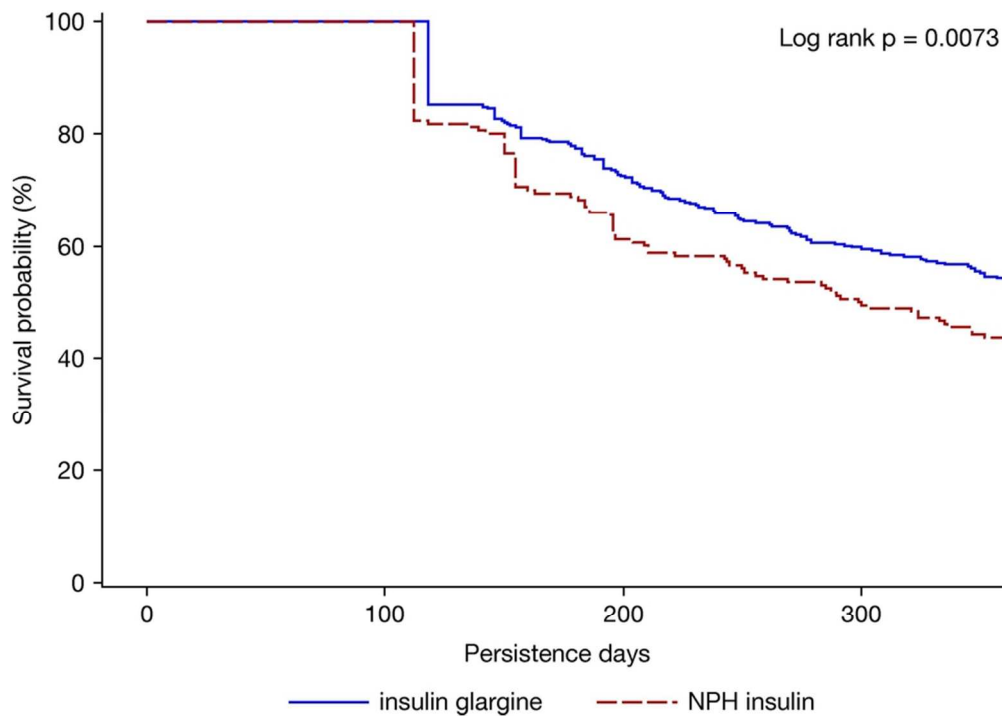
Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

\*P<0.05 vs insulin glargine

58x36mm (300 x 300 DPI)

Review only

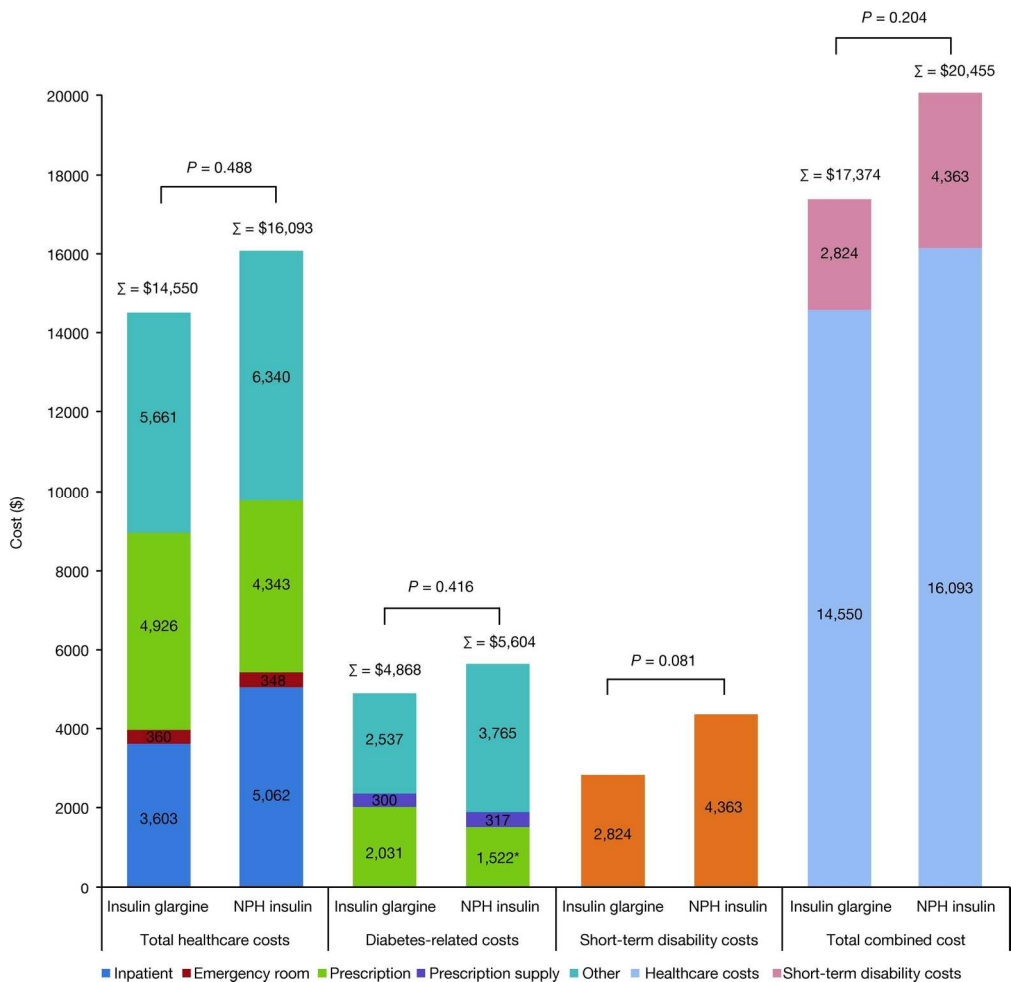
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Kaplan-Meier Curve of follow-up 1 Year persistence days between insulin glargine and NPH insulin  
81x57mm (300 x 300 DPI)

view only





1-year short-term disability and direct healthcare costs. (Total between-group differences did not reach statistical significance).

\*P<0.0001 vs insulin glargine 181x175mm (300 x 300 DPI)



**Additional File 1**

EVEREST Statement: Checklist for health economics paper

	<b>Study Section</b>	<b>Additional Remarks</b>
<b>Study Design</b>		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction/Methods/discussion	
(6) The form of economic evaluation used is stated	Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction/Methods/discussion	
<b>Data Collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods/results	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	Methods/Results	
(14) Productivity changes (if included) are reported	Results/Methods	Effect on productivity

	Study Section	Additional Remarks
separately		is estimated by the length/cost of claims for short term disability
(15) The relevance of productivity changes to the study question is discussed	Introduction/discussion	
(16) Quantities of resources are reported separately from their unit costs	N/A	
(17) Methods for the estimation of quantities and unit costs are described	N/A	
(18) Currency and price data are recorded	Results	
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
<b>Analysis and Interpretation of Results</b>		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods/Results	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	Results	
(30) Relevant alternatives are compared	Results	

	<b>Study Section</b>	<b>Additional Remarks</b>
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results/discussion	
(34) Conclusions follow from the data reported	Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	



**Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study**

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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics
Keywords:	healthcare utilization, employee productivity, diabetes costs

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**Title:**

Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study

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**Word count:** 3,158

## Article Summary

### Article Focus

- Do differences seen in the outcomes of randomized controlled trials comparing insulin glargine and neutral protamine Hagedorn (NPH) translate to improved real-world outcomes in employed adults living in the United States?

### Key Messages

- Insulin glargine was associated with better persistence, lower inpatient admission, which offsets its higher drug cost, and lower indirect costs from short-term disability, than NPH insulin.
- Reduced short-term disability and improved adherence with insulin glargine may improve long-term productivity, compared with NPH insulin, and provide benefits to both employees and their employers.

### Strengths and Limitations

- *Strengths*
  - The MarketScan database represents a large and diverse data source.
  - The database captures detailed information on both employees' healthcare resource utilization and their productivity, as measured by short-term-disability.
  - The use of propensity-score-matching methodology reduces confounding by indication as treatment selection bias between insulin glargine and NPH groups.
  - Sensitivity analysis confirmed the consistency of findings.
- *Limitations:*
  - As with all retrospective studies, causality of treatment effects cannot be established in this study. This study used a convenience sample, so it is not representative of the overall US population, and also may be underpowered to detect all significant differences between groups.
  - It is unlikely that rates of hypoglycemia and other clinical outcomes would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, A1C data were not available, so neither the effectiveness of glycemic control nor its association with hypoglycemia, could be assessed.

**[Abstract]****Limit: 300 words****Current: 299 words**

**Objectives:** To compare real-world outcomes of initiating insulin glargine (GLA) versus neutral protamine Hagedorn (NPH) insulin among employees with type 2 diabetes mellitus (T2DM) who had both employer-sponsored health insurance and short-term-disability coverages .

**Design:** Retrospective cohort study

**Setting:** MarketScan Commercial Claims and Encounters/Health and Productivity Management Databases 2003–2009.

**Participants:** Adult employees with T2DM who were previously treated with oral antidiabetic drugs and/or glucagon-like-peptide 1 receptor agonists, and initiated GLA or NPH were included if they were continuously enrolled in healthcare and short-term-disability coverages for 3 months before (baseline) and 1-year after (follow-up) initiation. Confounding by indication was addressed by 2:1 propensity score matching (PSM). Sensitivity analyses were conducted using different matching ratios.

**Primary and secondary outcome measures:** Outcomes during 1-year follow-up were measured and compared: insulin treatment persistence and adherence; hypoglycemia rates and daily average consumption of insulin; total and diabetes-specific healthcare resource utilization and costs; and loss in productivity, as measured by short-term disability, and the associated costs.

**Results:** A total of 534 patients were matched and analyzed (GLA: 356; NPH 178) with no significant differences in baseline characteristics. GLA patients were more persistent and adherent (both  $P < 0.05$ ), had lower rates of hospitalization (23.0% vs 31.4%;  $P = 0.036$ ) and endocrinologist visits (19.1% vs 26.9%;  $P = 0.038$ ), similar hypoglycemia rates (both 4.4%;  $P = 1.0$ ), higher diabetes drug costs (\$2,031 vs \$1,522;  $P < 0.001$ ), but similar total healthcare costs (\$14,550 vs \$16,093;  $P = 0.448$ ) and total diabetes-related healthcare costs (\$4,686 vs \$5,604;  $P = 0.416$ ). Short-term disability days and costs were numerically lower in the GLA



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3 cohort (16.0 vs 24.5 days; P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively). Sensitivity  
4 analysis yielded similar findings.  
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8 **Conclusion:**

9 Insulin glargine results in better persistence and adherence, compared with NPH insulin,  
10 with no overall cost disadvantages. Better persistence and adherence may lead to long-term  
11 health benefits for employees with T2DM.  
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## INTRODUCTION

In the United States (US), diabetes affects an estimated 25.8 million people (8.3% of the US population).[1] Type 2 diabetes mellitus (T2DM) and associated comorbidities are associated with disability, reduced productivity, and work loss,[2, 3] which impose an important economic burden on self-insured employers.[4] The diabetes-related economic burden from lost productivity and disability for employees and employers is substantial. Overall, reduced national productivity related to diabetes accounted for \$58 billion in 2007 in the US,[5] while in a more recent study diabetes accounted for 1,473,000 disability-adjusted life years.[6]

A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides clinically relevant improvements in glycemic control with a good safety profile.[7] In addition, early improvements in glucose control can reduce the long-term risk of complications.[8] Options for basal insulin include insulin glargine, a long-acting basal insulin analog, or Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting insulin. Clinical studies have shown that the efficacy of these two agents is similar, but that there is a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, with insulin glargine.[9-11]

Simplicity and convenience of treatment regimens are important for those initiating insulin therapy. Insulin glargine was approved for once-daily injection and may have implications for increased patient persistence and adherence.[12] Although, twice-daily use of insulin glargine might be required to achieve therapeutic goals in some patients with T2DM.[13] Adherence is also associated with improved glycemic control and decreased healthcare resource utilization[14] and, consequently, may improve outcomes. Other insulin therapy options, such as insulin detemir and insulin lispro protamine suspension, also have convenience and outcomes benefits which may contribute to improved persistence and adherence.[15-17]. In reality, patients taking insulin glargine have been shown to be more likely to persist with their medication than those taking NPH insulin.[18] In general, treatment complexity for chronic conditions – including, though not limited to the need to administer more than one injection daily – correlates with poor adherence.[19]

Adherence to medication also reduces the incidence of complications, and is thus associated with improved work-related outcomes, such as reducing the number of short-term disability days.[20] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[21, 22] People with untreated diabetes, or those with a long duration of the disease, are at increased risk of occupational injury, which is minimized in treated patients

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3 who are adherent to medication.[23] Effective pharmacological management of diabetes with  
4 adequate compliance also results in substantial cost benefits to employers.[21, 24]  
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7 Although there are data in support of the clinical benefits of basal insulins there is currently a  
8 paucity of real-world information about the impact of different basal insulin regimens on  
9 healthcare utilization, employee disability, and their associated costs from an employer's  
10 perspective.  
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## 13 14 15 **METHODS**

### 16 **Database**

17 This study is a retrospective analysis from the employer perspective, of patients' medical  
18 and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters  
19 Database 2003–2009. This database captures person-specific clinical utilization,  
20 expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out  
21 services from about 100 large employers, health plans, and government and public  
22 organizations.  
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28 Short-term disability data were extracted from the MarketScan Health and Productivity  
29 Management Database, which is an integrated database that contains information on  
30 absence, short-term disability, and workers' compensation experience. This information is  
31 linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial  
32 Claims and Encounters Database for these employees, providing a unique and valuable  
33 resource for examining health and productivity issues for an employed, privately insured  
34 population.  
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40 The MarketScan Research Databases are fully compliant with the letter and spirit of the  
41 Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board  
42 review was waived.  
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### 47 **Cohort selection criteria**

48 Included in the analysis were employees, but not their dependents, of 18 years of age or  
49 older with T2DM, defined as having made at least one inpatient visit or two physician visits  
50 dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type  
51 II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th  
52 Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or  
53 unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine  
54 or NPH insulin with the date of the first such claim being the index date (prescriptions of  
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3 other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare  
4 benefits and work benefits for short-term disability for 3 months prior to insulin initiation  
5 (baseline period), and 12 months after insulin initiation (follow-up period); and on at least one  
6 oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The  
7 patient cohorts for comparison were determined on the basis of use of insulin glargine or  
8 NPH insulin at initiation of insulin therapy. Outcomes were compared between the matched  
9 cohorts after 1 year of follow-up.  
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### 14 **Baseline characteristics**

15 Data were analyzed to assess baseline characteristics, including: gender; age; OAD use;  
16 comorbidities; healthcare utilization/costs; and short-term disability for 3 months prior to  
17 insulin initiation for all patients. Follow-up records were analyzed to assess treatment  
18 persistence, adherence, hypoglycemic events, healthcare resource utilization, cost, and  
19 short-term disability after initiation of insulin therapy.  
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### 26 **Persistence and Adherence**

27 Measuring persistence with insulin treatment is challenging due to its non-fixed dose  
28 schedule. Consistent with previously published studies,[25-27] persistence was measured  
29 here as the time the patient had remained on study drugs without discontinuation or  
30 switching following insulin initiation. Study medication was considered discontinued if the  
31 prescription was not refilled within the expected time of medication coverage, defined as the  
32 90th percentile of the time, stratified by the metric quantity supplied, between the first and  
33 second fills among patients with at least one refill. For example, our analysis showed that for  
34 patients who filled prescription for 10 mL and refilled later, 90% of GLA patients refilled it  
35 within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered  
36 discontinuing GLA if he/she previously filled a prescription for 10mL of GLA but did not refill it  
37 within 119 days. Patients who restarted their initial medication after discontinuation, as  
38 defined above, were also considered non-persistent patients. Sensitivity analyses were also  
39 conducted using the 75th and 95th percentiles of the time.  
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48 Treatment adherence was measured during the 1-year follow-up by both the traditional  
49 medication possession ratio (MPR) and the adjusted MPR, which allows for differences in  
50 insulin-device package size [28] (insulin glargine, for example, is packaged either in 10 mL  
51 vials with a total of 1,000 units, or in a 3 mL disposable device in a package of 5 pens with a  
52 total of 1,500 units) to correct the issue that almost all prescriptions are dispensed with a 30-  
53 day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying  
54 the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in  
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3 the analysis period divided by the number of days in the analysis period) by the average  
4 number of days between insulin study drug prescription refills for patients using the insulin  
5 divided by the average days' supply for patients using the insulin. By using data based on  
6 the actual gap between the days' supply and the days to next refill, this adjustment is  
7 necessary to measure real adherence to doctor's instructions.  
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### 10 11 12 **Clinical outcomes**

13 Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency  
14 department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia  
15 (ICD-9 code 250.8—diabetes with other specified manifestations; 251.0—hypoglycemic coma;  
16 251.1—other specified hypoglycemia; or 251.2—hypoglycemia, unspecified).[29] Daily  
17 average consumption (DACON) of insulin was estimated based on pharmacy claim data and  
18 calculated as the total number of units dispensed before the last refill of study drug divided  
19 by the total number of days between initiation and last refill during follow-up period. A1C  
20 data were not available in this study.  
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### 27 28 **Healthcare resource utilization and cost**

29 Categories of healthcare resource utilization included numbers of outpatient visits,  
30 emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total  
31 outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare  
32 resource utilization included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx),  
33 and use of anti-hyperglycemic medications, glucose meters and supplies.  
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38 Healthcare costs were computed as paid amounts of adjudicated claims, including insurer  
39 and health-plan payments, copayments and deductibles. Diabetes-specific healthcare costs  
40 included those related to a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx).  
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### 45 **Loss in productivity and its associated costs**

46 Loss in productivity was measured by the total number of days patients were on short-term  
47 disability during the baseline and follow-up periods. The associated costs for short-term  
48 disability were calculated as 70% of \$240 (a figure reflecting the average daily wage paid to  
49 employees of large employers),[30] which amounts to \$168, since disability programs  
50 typically pay for 70% of lost income.[31]  
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### 55 **Total cost**

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3 Total cost was assessed by combining direct costs (healthcare) and indirect costs (short-  
4 term disability costs), and comparisons between groups were made. Costs were adjusted for  
5 inflation to 2010 US dollars using the medical care component of the Consumer Price Index.  
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### 8 9 **Statistical analyses**

10 To reduce the observed baseline selection bias, such as confounding by indication,  
11 between the two study cohorts, propensity score matching (PSM) methodology [32] was  
12 implemented, with a stringent 2:1 matching of patients initiating insulin glargine or NPH  
13 insulin. Propensity scores for initiating insulin glargine vs NPH were calculated from a logistic  
14 regression model that estimated the likelihood of initiating insulin glargine based on the  
15 observed patient characteristics. Covariates were selected based on their hypothesized  
16 confounding relationship with the outcome variables, and included age, gender, region,  
17 health plan type, Charlson Comorbidity Index, and baseline concomitant medications,  
18 hypoglycemic events, healthcare utilization (overall or disease-related), co-pays, and  
19 healthcare cost (overall or disease-related). Sensitivity analyses were also conducted using  
20 1:1 and 3:1 PSM.  
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29 Among the matched cohorts, all study variables, including baseline and outcome measures,  
30 were analyzed descriptively. Results were stratified by treatment cohort. For dichotomous  
31 variables, P values were calculated according to the Mann–Whitney U test; for continuous  
32 variables, t tests were used to calculate P values. P values of <0.05 were taken to be  
33 indicative of a significant difference. Kaplan–Meier survival curve and the log-rank test were  
34 used to compare 1-year treatment persistence. The relationship between hospitalization and  
35 short-term disability was investigated by the chi-squared test and Pearson's correlation  
36 analysis.  
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## 42 **RESULTS**

### 43 **Baseline characteristics**

44 Data from 2,454 patient records were eligible for the 1-year follow-up analyses: 2,250 in the  
45 insulin glargine (GLA) cohort, and 204 in the NPH insulin (NPH) cohort. Before the matching,  
46 GLA patients were more likely to be male, older, using insulin pen, and had higher  
47 copayment than NPH patients (data not shown here), indicating confounding by indication as  
48 selection bias. The 2:1 PSM yielded a total of 534 patients (GLA: 356; NPH 178) with well-  
49 matched baseline characteristics (table 1). Overall, 43.8% of the patients included in the  
50 analysis were women; mean age was 49 years (range: 20–64 years), and the mean number  
51 of OADs was 1.8. The baseline hospitalization rate was 15.2%, with a mean short-term  
52 disability of 3.0 days.  
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**Table 1.** Baseline characteristics (3 months prior to index)

	<b>Insulin glargine (n=356)</b>	<b>NPH insulin (n=178)</b>	<b>P value</b>
Gender, female (%)	153 (42.9%)	81 (45.5%)	0.5789
Age, years, mean ± SD	49 ± 10	49 ± 10	0.7580
	18–39, n (%)	35 (19.6%)	0.5988
	40–64, n (%)	143 (80.3%)	0.5988
Health plan, n (%)			0.9390
	CDHP	5 (1.4%)	2 (1.1%)
	Comprehensive	34 (9.5%)	18 (10.1%)
	HMO	63 (17.6%)	36 (20.2%)
	POS	65 (18.2%)	29 (16.2%)
	PPO	189 (53.0%)	93 (52.2%)
Region, n (%)			
	North Central Region	82 (23.0%)	45 (25.2%)
	Northeast Region	58 (16.2%)	32 (17.9%)
	South Region	129 (36.2%)	54 (30.3%)
	West Region	85 (23.8%)	45 (25.2%)
	Unknown	2 (0.5%)	2 (1.1%)
Insulin Pen use, n (%)	59 (16.5%)	33 (18.5%)	
Antidiabetic drugs, n (%)			
	Metformin	262 (73.5%)	132 (74.1%)
	Sulfonylureas	223 (62.6%)	105 (58.9%)
	Thiazolidinediones	133 (37.3%)	68 (38.2%)
	DPP-4 inhibitors	9 (2.5%)	6 (3.3%)
	Exenatide	30 (8.4%)	11 (6.1%)
Number of OADs, mean ± SD	1.81 ± 0.73	1.80 ± 0.75	0.9015
Charlson Comorbidity Index, mean ± SD	0.284 ± 0.819	0.281 ± 1.159	0.9770
Comorbidities, n (%)			
	Obesity	5 (1.4)	4 (2.2)
	Hypertension	76 (21.3)	39 (21.9)
	Hyperlipidemia	39 (10.9)	22 (12.3)
	Congestive heart failure	12 (3.3)	4 (2.2)
	Retinopathy	7 (1.9)	5 (2.8)
	Neuropathy	19 (5.3)	8 (4.4)
	Nephropathy	15 (4.2)	3 (1.6)
Total healthcare utilization, n (%) or mean ± SD [median]			
	Hospitalizations	53 (14.8%)	28 (15.7%)
	Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]
	ER visits	80 (22.4%)	38 (21.3%)
	Endocrinologist visits	38 (10.6%)	25 (14.0%)
	Hospitalization/patient	0.16 ± 0.39 [0]	0.17 ± 0.42 [0]
	ER visits/patient	0.31 ± 0.67 [0]	0.28 ± 0.68 [0]
	Endocrinologist visits/patient	0.15 ± 0.48 [0]	0.19 ± 0.55 [0]
Diabetes-related healthcare utilization, n (%) or mean ± SD [median]			
	Hospitalizations	34 (9.5%)	20 (11.2%)
	ER visits	37 (10.3%)	17 (9.5%)
	Endocrinologist visits	36 (10.1%)	23 (12.9%)
	Office visits	297 (83.4%)	138 (77.5%)
	Hospitalizations/patient	0.10 ± 0.29	0.11 ± 0.32
	ER visits/patient	0.13 ± 0.40 [0]	0.11 ± 0.34 [0]
	Endocrinologist visits/patient	0.14 ± 0.47 [0]	0.17 ± 0.53 [0]
	Office visits/patient	1.74 ± 1.43 [1]	1.60 ± 1.44 [1]
	Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean ± SD [median]			
	Inpatient cost	2756 ± 12393 [0]	1958 ± 8241 [0]
	Outpatient cost	1385 ± 3652 [498]	1766 ± 4243 [613]
	ER cost	181 ± 476 [0]	144 ± 515 [0]
	Prescription cost	937 ± 1236 [677]	926 ± 1065 [699]



	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Total cost	5259 ± 14237 [1632]	4794 ± 10731 [1895]	0.6735
Total diabetes-related healthcare cost, mean ± SD [median]			
Inpatient cost	1304 ± 6588 [0]	811 ± 3447 [0]	0.2570
Outpatient cost	242 ± 321 [158]	274 ± 505 [131]	0.4393
ER cost	46 ± 216 [0]	34 ± 195 [0]	0.5346
Prescription cost	294 ± 293 [204]	285 ± 309 [154]	0.7474
Supply cost	48 ± 97 [0]	46 ± 92 [0]	0.7766
Total cost	1934 ± 6551 [621]	1450 ± 3485 [596]	0.2658
Co-pay, n (%)			
\$0–\$15	166 (46.6%)	87 (48.8%)	0.8694
\$15–\$30	147 (41.2%)	71 (39.8%)	
\$30+	42 (11.7%)	20 (11.2%)	
Unknown	1 (0.2%)	0 (0.0%)	
Short-term disability, mean ± SD			
Occurrence count	0.12 ± 0.34	0.12 ± 0.37	0.9310
Days	3.10 ± 12.97	2.98 ± 12.9	0.9153
Cost	538 ± 2250	534 ± 2349	0.9856
Total cost (healthcare + short-term disability), mean ± SD	5797 ± 15005	5328 ± 12174	0.6987

Baseline information is collected within 3 months prior to index date. CDHP, consumer-driven health plan; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; ER, Emergency Room; HMO, health maintenance organization; NPH, neutral protamine Hagedorn insulin; OADs, oral antidiabetic drugs; POS point of service; PPO, preferred provider organization; SD, standard deviation.

### Persistence and adherence

During the 1-year follow-up, patients receiving insulin glargine were significantly more persistent (table 2, figure 1) and adherent compared with those in the NPH insulin cohort (table 2). Over half (54.5%) of patients on insulin glargine were persistent, compared with 43.8% of those on NPH (P=0.0225). Patients stayed on insulin glargine treatment for a significantly longer period (approximately 22 days longer) than those on NPH insulin (284 vs 262 days, P=0.0178). The Kaplan–Meier survival curve shows that patients treated with NPH discontinued sooner than those treated with insulin glargine (log-rank test P-value=0.0073; figure 2). Sensitivity analyses using the 75th and 95th percentiles yielded similar results, with all indicating better persistence with insulin glargine compared with NPH insulin (75th percentile: 34.0% vs 28.1%, P=0.17; 95th percentile: 67.2% vs 57.9%, P=0.039). Both traditional and adjusted MPR values indicated a significantly better adherence to treatment with insulin glargine, compared with NPH insulin (table 2, figure 1).

**Table 2. Follow-up treatment persistence, hypoglycemia, healthcare utilization and loss in productivity**

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Persistence/adherence, n (%) or mean ± SD			
Treatment persistence	186 (54.5)	75 (43.8)	0.0225



	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Treatment persistence days	283.85 ± 96.92	261.77 ± 103.35	0.0178
MPR,	0.50 ± 0.28	0.45 ± 0.30	0.0418
Adjusted MPR	0.67 ± 0.33	0.61 ± 0.35	0.0380
DACON	30.6 ± 21.1	35.8 ± 31.9	0.0740
<b>Hypoglycemia, n (%) or mean ± SD</b>			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
<b>Total healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	82 (23%)	56 (31.4%)	0.0360
ER visits	104 (29.2%)	57 (32.0%)	0.5049
Endocrinologist visits	68 (19.1%)	48 (26.9%)	0.0377
Office visits	352 (98.8%)	177 (99.4%)	0.5251
Hospitalizations/patient	0.28 ± 0.58 [0]	0.41 ± 0.73 [0]	0.0353
ER visits/patient	0.56 ± 1.43 [0]	0.54 ± 1.03 [0]	0.8353
Endocrinologist visits/patient	0.61 ± 1.57 [0]	0.94 ± 1.84 [0]	0.0422
Office visits/patient	18.37 ± 17.43 [14]	18.30 ± 14.98 [14]	0.9615
Total hospitalization days	1.29 ± 4.54 [0]	2.06 ± 4.98 [0]	0.0754
<b>Diabetes-related healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	45 (12.6%)	27 (15.1%)	0.4201
ER visits	43 (12.0%)	27 (15.1%)	0.3186
Endocrinologist visits	68 (19.1%)	45 (25.2%)	0.0993
Office visits	341 (95.7%)	168 (94.3%)	0.4689
Hospitalizations/patient	0.14 ± 0.38 [0]	0.15 ± 0.36 [0]	0.6801
ER visits/patient	0.20 ± 0.81 [0]	0.16 ± 0.40 [0]	0.5207
Endocrinologist visits/patient	0.56 ± 1.45 [0]	0.80 ± 1.65 [0]	0.1100
Office visits/patient	5.69 ± 3.98 [5]	5.56 ± 4.23 [5]	0.7293
Total hospitalization days	0.56 ± 2.50 [0]	0.53 ± 1.99 [0]	0.8659
<b>Loss in productivity, mean ± SD</b>			
Short-term disability occurrences	0.36 ± 0.70	0.38 (0.70)	0.7944
Short-term disability days	15.96 ± 38.78	24.51 ± 60.33	0.0862

DACON, daily average consumption; ER, Emergency Room; NPH, neutral protamine Hagedorn insulin; SD, standard deviation

### Clinical outcomes

Clinical outcomes of the two agents were similar, both in terms of hypoglycemia-related event rates (both cohorts had overall hypoglycemia rates of 4.4%; P=1.0) and DACON (insulin glargine: 30.6 units vs NPH insulin: 35.8 units, P=0.074) (table 2).

### Healthcare utilization and cost

In terms of total healthcare utilization and cost, patients in the insulin glargine cohort also had lower rates of hospitalization, compared with those in the NPH insulin cohort (23.0% vs 31.4%; P=0.036, respectively; table 2), and of endocrinologist visits (19.1% vs 26.9%; P=0.038), despite similar utilization at baseline (table 1). All diabetes-related healthcare utilization outcomes were similar between the cohorts (table 2). With respect to cost outcomes, the total overall healthcare costs were similar for the insulin glargine and NPH insulin cohorts (\$14,550 vs \$16,093, respectively; P=0.448), as were total diabetes-related healthcare costs (\$4,686 vs \$5,604; P=0.416) (figure 3). Similar total diabetes-related healthcare costs were reported despite significantly higher diabetes-related prescription

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3 costs for the insulin glargine cohort (\$2,031), compared with the NPH insulin cohort (\$1,522)  
4 (P<0.001).  
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### 7 **Loss in productivity and its associated costs**

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9 In terms of loss in productivity and the associated costs for employers, the incidence of  
10 claims for short-term disability was 0.36 per patient per year in the insulin glargine group,  
11 compared with 0.38 in the NPH insulin group (P=0.7944). However, the total number of  
12 short-term disability days and the associated cost were numerically lower in the insulin  
13 glargine group (16.0 vs 24.5 days; P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively.  
14 figure 3). Combined total costs were similar between the insulins (\$17,374 for GLA vs  
15 \$20,455 for NPH, P=0.204).  
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### 20 **Correlations**

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22 In the 2:1 matched cohorts, the chi-squared tests showed that patients who were not  
23 persistent with their insulin treatment were significantly more likely to have a claim for short-  
24 term disability (33.47% vs. 22.22%, P=0.0045), and so were those with hospitalizations  
25 (60.1% vs. 15.7%, P <0.001). Pearson's correlation test showed that higher number of  
26 insulin persistence days was correlated with lower number of short-term-disability days (r=-  
27 0.1325, P=0.0027), while higher number of hospitalizations was correlated with higher  
28 number of short-term disability claims (r=0.40, P<0.0001).  
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### 39 **Sensitivity analysis**

40 The sensitivity analyses using 1:1 and 3:1 PSM yielded similar results overall. In the 1:1  
41 PSM analysis (n=199, both cohorts), persistence with treatment was higher with insulin  
42 glargine than with NPH insulin (75th percentile: 32.8% vs 26.0%, P=0.146; 90th percentile:  
43 51.0% vs 41.1%, P=0.052; 95th percentile: 66.1% vs 54.6%, P=0.022). Treatment adherence  
44 was also higher with insulin glargine than with NPH insulin (MPR: 0.49 vs 0.43, P=0.039;  
45 adjusted MPR: 0.66 vs 0.60; P=0.070). A significantly lower hospitalization rate (26.1% vs  
46 36.1%, P=0.030), lower endocrinologist visit rate (17.0% vs 26.1%, P=0.028), fewer  
47 hospitalization days (1.32 vs 2.29 days, P=0.026), fewer short-term disability days and lower  
48 associated costs (12.33 days vs 27.67 days; P=0.002 and \$2,173 vs \$4,942; P=0.002,  
49 respectively) were reported with insulin glargine than with NPH insulin in the 1:1 PSM  
50 analysis. Total costs in the 1:1 matched cohort were also significantly lower in the GLA  
51 cohort than in the NPH cohort (\$15,720 vs \$21,398, P=0.022). The results from the 3:1 PSM  
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3 analysis (n=480, insulin glargine; n=160, NPH insulin) were consistent with those from the  
4 2:1 PSM analysis.  
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## 7 **DISCUSSION**

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9 In this real-world study, use of insulin glargine was associated with better persistence and  
10 adherence than NPH insulin. In addition, a lower healthcare resource utilization was  
11 associated with insulin glargine than NPH insulin, in terms of hospitalizations and  
12 endocrinologist visits, over 1 year of follow-up. Rates of hypoglycemia-related events were  
13 similar with the two treatments. Furthermore, diabetes drug-related costs were higher with  
14 insulin glargine than with NPH insulin, likely due to higher drug price of insulin glargine, and  
15 also the improved persistence/adherence associated with it. However, both total diabetes-  
16 related and total healthcare costs were similar in the two groups, as a consequence of the  
17 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated  
18 with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations  
19 and endocrinologist visits were also numerically lower in GLA group but not statistically  
20 significant, probably due to sample size and the inaccuracy of using ICD-9-CM diagnosis  
21 code (250.xx) to capture diabetes-related events. In regard to short-term disability in both  
22 primary and sensitivity analyses, numerically fewer short-term disability days and lower  
23 associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort,  
24 but this was not significant. It is likely that the reduction in short-term disability is related to  
25 fewer hospitalizations in the insulin glargine cohort. Indeed, the correlation analysis showed  
26 that patients with any hospitalizations were significantly more likely to claim for short-term  
27 disability: both the number and duration of hospitalizations were highly correlated with the  
28 number of claims and the duration of short-term disability.  
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41 A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in  
42 patients with T2DM have indicated that insulin glargine represents an economic treatment  
43 option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at  
44 least as effective glycemic control as NPH insulin, and to be cost effective in a range of  
45 countries and settings.[33-39]  
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50 Basal insulin analogs have been shown to have several advantages compared to NPH  
51 insulin including less pharmacologic variability, lower risk of hypoglycemia, and greater  
52 impact on quality of life.[14-16, 40] The rates of hypoglycemia-related events were, however,  
53 similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated  
54 with less hypoglycemia than NPH insulin,[15] the switch from NPH insulin to insulin glargine  
55 may usually be considered in patients with evidence of hypoglycemia or increasing incidence  
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3 of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this  
4 study were similar, and thus it is possible that the NPH insulin cohort in the present analysis  
5 may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.  
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9 The increased persistence associated with insulin glargine, as shown in this study, may lead  
10 to better clinical outcomes,[41] and potentially improve work-related outcomes.[13, 20, 23]  
11 Diabetes-related disability has been shown to result in loss of work place productivity.[42-46]  
12 In this study, we observed fewer short-term disability days in patients on insulin glargine,  
13 compared with those on NPH insulin. Although the differences were not statistically  
14 significant, this finding may suggest that initiation of therapy with insulin glargine could help  
15 increase workplace productivity among employed patients with T2DM compared with those  
16 initiating with NPH insulin.  
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23 As with all retrospective studies, issues of sampling bias should be taken into account when  
24 interpreting these results, which may introduce selection bias. The use of PSM methodology  
25 in this study should have helped reduce the impact of selection bias such as confounding by  
26 indication. In fact, three different matching ratios were tested, and all yielded similar findings.  
27 However, it likely limited patients in the insulin glargine cohort to those most similar to the  
28 NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further,  
29 some insulin patients may have been missed due to the availability of 90 day/mail order  
30 prescriptions resulting in them being missed during the 3 month baseline period.  
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37 This study has several limitations. Although the MarketScan data represent a large diverse  
38 population, it only included information from mainly large, self-insured employers, whose  
39 employees were more likely to locate in certain geographic areas than the general employee  
40 population, and the analysis included a convenience sample of patients whose employer  
41 supplied productivity data. Therefore, this study should not be assumed as representative of  
42 the overall US population. As any retrospective observational study, causality of treatment  
43 effects cannot be established in this study. Although the PSM method was used to reduce  
44 the treatment selection bias issues such as confounding by indications, it also led to  
45 significant reduction in the sample size, particularly on the GLA group, due to the required  
46 matching ratios, and relatively much smaller sample size in NPH group. This may also  
47 makes the study underpowered to detect all significant differences between treatment  
48 groups. In addition, the similar rate of hypoglycemia observed between groups is  
49 inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia  
50 with insulin glargine, compared with NPH insulin.[9, 33] It is unlikely that rates of  
51 hypoglycemia would be captured with the same level of sensitivity in this retrospective  
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3 analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia  
4 rate in both cohorts may have resulted in insufficient statistical power to detect significant  
5 differences. Coding issues in the claim data may also have contributed to the lack of  
6 statistical robustness. The daily units of insulin (DACON) was measured based on pharmacy  
7 claim data and may not be accurate. For example, patients on a low dose are instructed to  
8 discard unused insulin (particularly in vials) after approximately 1 month, hence, pharmacy  
9 claim data can lead to an overestimation of DACON. However, this is unlikely to affect GLA  
10 and NPH groups disproportionately because they were similar in proportion of patients using  
11 insulin pens (Table 2). A1C data were not available, so neither the effectiveness of glycemic  
12 control nor the association with hypoglycemia could be assessed. Finally, the 12 month  
13 follow-up period of this study may not have been sufficient to detect benefits due to improved  
14 persistence and adherence.  
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## 21 22 23 **CONCLUSION**

24 This study showed that insulin glargine resulted in better persistence and adherence, with  
25 lower health care utilization, at similar total healthcare costs despite higher drug-related  
26 costs, than NPH insulin. Better persistence and adherence may lead to long-term health  
27 benefits and additional benefits to patients with T2DM and their employers. Due to the  
28 retrospective nature of this study, further studies need to be conducted to confirm these  
29 findings.  
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## 35 36 37 **ACKNOWLEDGEMENTS**

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39 support in the preparation of this manuscript from Ewen Legg, PhD, of Excerpta Medica.  
40

## 41 42 43 **DISCLOSURES**

44 LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis  
45 U.S.

46 RM and WW: Employees of sanofi-aventis U.S.  
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## 50 51 52 **CONTRIBUTIONS**

53 LW: Active in study design, statistical plan, data analysis, drafting, and review of manuscript.

54 WW: Active in creating the concept and study design, drafting, and review of manuscript.

55 RM: Active in creating the concept and study design, drafting, and review of manuscript.

56 LX: Role in statistical analysis and review of manuscript.

57 OB: Active in creating the study design, statistical plan, and review of manuscript.  
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**DATA SHARING**

Additional data is available by e-mailing Dr Onur Baser [obaser@statinmed.com](mailto:obaser@statinmed.com)

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3 **Figure legends**

4 **Figure 1** Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

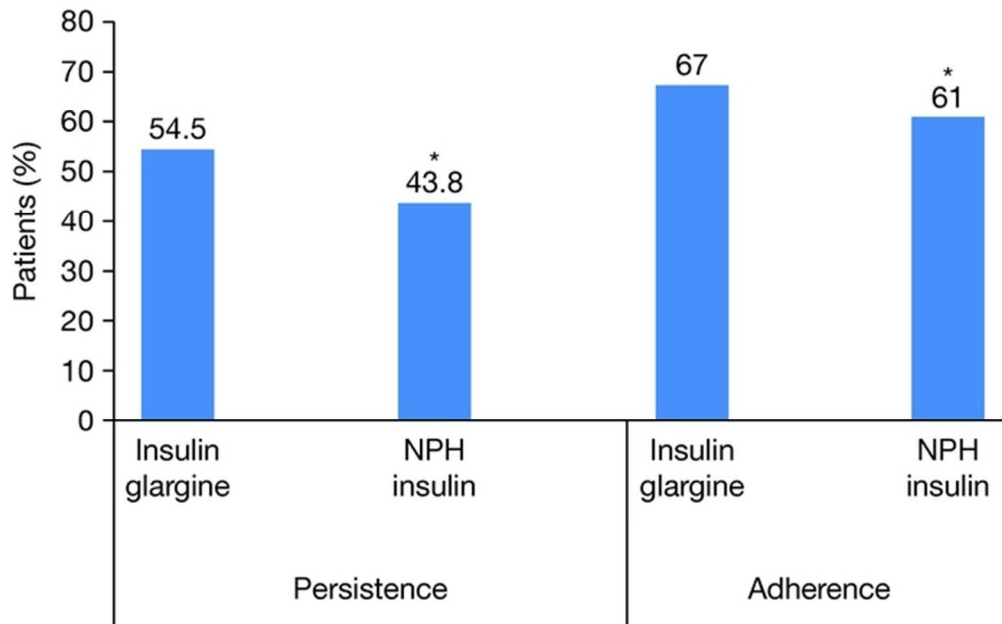
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7 \*P<0.05 vs insulin glargine

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11 **Figure 2** Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine  
12 and NPH insulin

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17 **Figure 3** 1-year short-term disability and direct healthcare costs. (Total between-group  
18 differences did not reach statistical significance).

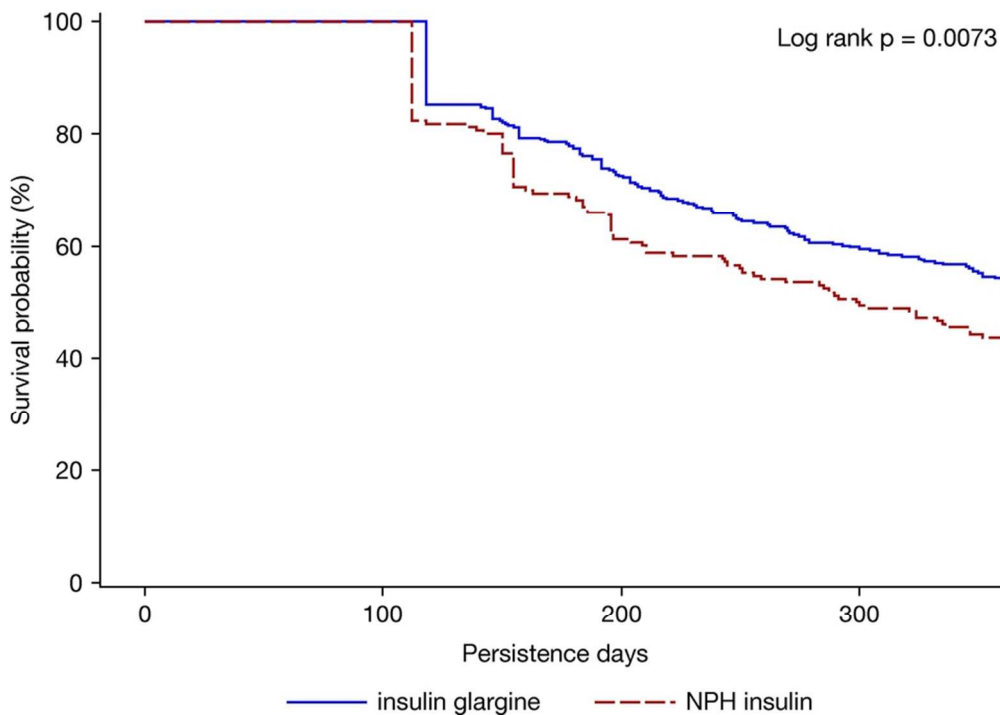
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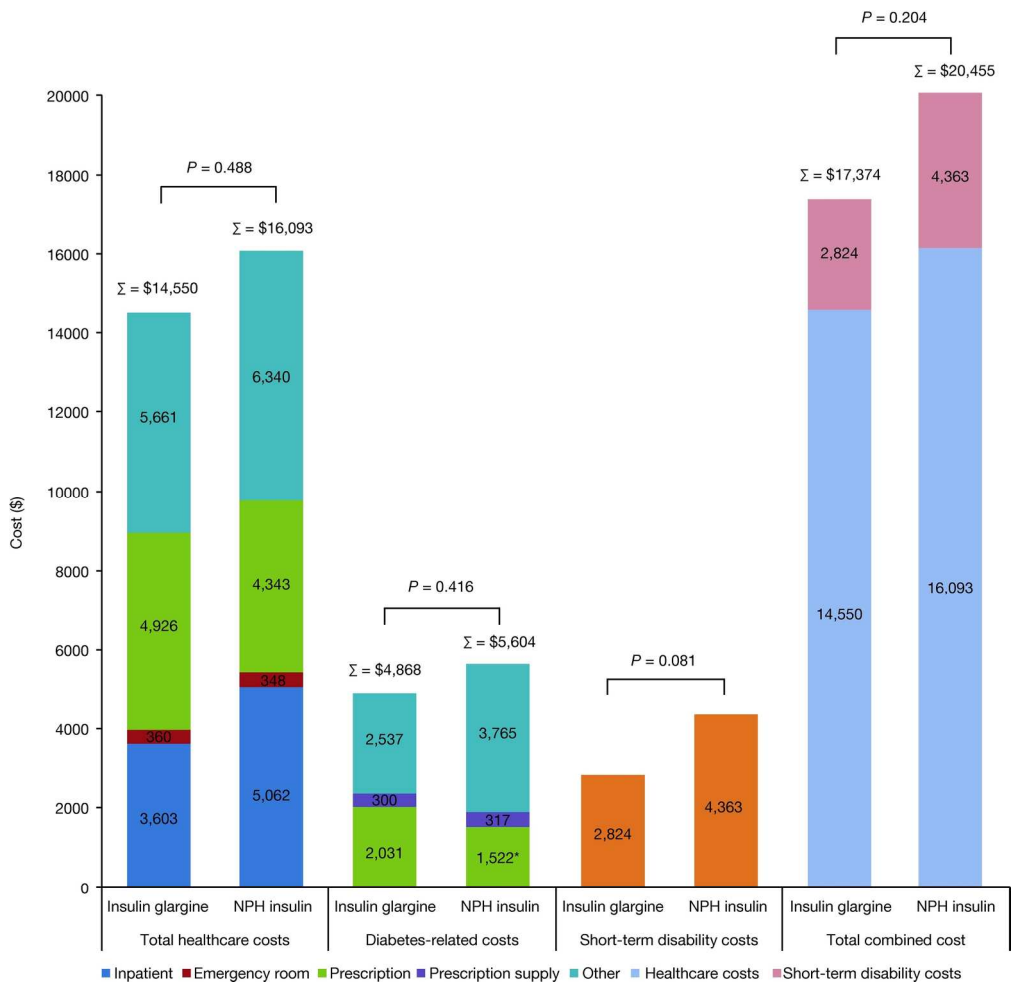
Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.  
\*P<0.05 vs insulin glargine  
58x36mm (300 x 300 DPI)

Review only



Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine and NPH insulin  
81x57mm (300 x 300 DPI)

view only



1-year short-term disability and direct healthcare costs. (Total between-group differences did not reach statistical significance).

\*P<0.0001 vs insulin glargine  
181x175mm (300 x 300 DPI)



**Additional File 1**

EVEREST Statement: Checklist for health economics paper

	<b>Study Section</b>	<b>Additional Remarks</b>
<b>Study Design</b>		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction/Methods/discussion	
(6) The form of economic evaluation used is stated	Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction/Methods/discussion	
<b>Data Collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods/results	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	Methods/Results	
(14) Productivity changes (if included) are reported	Results/Methods	Effect on productivity

	Study Section	Additional Remarks
separately		is estimated by the length/cost of claims for short term disability
(15) The relevance of productivity changes to the study question is discussed	Introduction/discussion	
(16) Quantities of resources are reported separately from their unit costs	N/A	
(17) Methods for the estimation of quantities and unit costs are described	N/A	
(18) Currency and price data are recorded	Results	
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
<b>Analysis and Interpretation of Results</b>		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods/Results	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	Results	
(30) Relevant alternatives are compared	Results	



	<b>Study Section</b>	<b>Additional Remarks</b>
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results/discussion	
(34) Conclusions follow from the data reported	Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

**Title:**

Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study

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## Article Summary

### Article Focus

- Do differences seen in the outcomes of randomized controlled trials comparing insulin glargine and neutral protamine Hagedorn (NPH) translate to improved real-world outcomes in employed adults living in the United States?

### Key Messages

- Insulin glargine was associated with better persistence, lower inpatient admission, which offsets its higher drug cost, and lower indirect costs from short-term disability, than NPH insulin.
- Reduced short-term disability and improved adherence with insulin glargine may improve long-term productivity, compared with NPH insulin, and provide benefits to both employees and their employers.

### Strengths and Limitations

- *Strengths*
  - The MarketScan database represents a large and diverse data source.
  - The database captures detailed information on both employees' healthcare resource utilization and their productivity, as measured by short-term-disability.
  - The use of propensity-score-matching methodology reduces **confounding by indication as treatment selection bias** between insulin glargine and NPH groups.
  - Sensitivity analysis confirmed the consistency of findings.
- *Limitations:*
  - As with all retrospective studies, causality of treatment effects cannot be established in this study. This study used a convenience sample, so it is not representative of the overall US population, and also may be underpowered to detect all significant differences between groups.
  - It is unlikely that rates of hypoglycemia and other clinical outcomes would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, A1C data were not available, so neither the effectiveness of glycemic control nor its association with hypoglycemia, could be assessed.

**[Abstract]****Limit: 300 words****Current: 299 words**

**Objectives:** To compare real-world outcomes of initiating insulin glargine (GLA) versus neutral protamine Hagedorn (NPH) insulin among employees with type 2 diabetes mellitus (T2DM) who had both employer-sponsored health insurance and short-term-disability coverages .

**Design:** Retrospective cohort study

**Setting:** MarketScan Commercial Claims and Encounters/Health and Productivity Management Databases 2003–2009.

**Participants:** Adult employees with T2DM who were previously treated with oral antidiabetic drugs and/or glucagon-like-peptide 1 receptor agonists, and initiated GLA or NPH were included if they were continuously enrolled in healthcare and short-term-disability coverages for 3 months before (baseline) and 1-year after (follow-up) initiation. Confounding by indication was addressed by 2:1 propensity score matching (PSM). Sensitivity analyses were conducted using different matching ratios.

**Primary and secondary outcome measures:** Outcomes during 1-year follow-up were measured and compared: insulin treatment persistence and adherence; hypoglycemia rates and daily average consumption of insulin; total and diabetes-specific healthcare resource utilization and costs; and loss in productivity, as measured by short-term disability, and the associated costs.

**Results:** A total of 534 patients were matched and analyzed (GLA: 356; NPH 178) with no significant differences in baseline characteristics. GLA patients were more persistent and adherent (both  $P < 0.05$ ), had lower rates of hospitalization (23.0% vs 31.4%;  $P = 0.036$ ) and endocrinologist visits (19.1% vs 26.9%;  $P = 0.038$ ), similar hypoglycemia rates (both 4.4%;  $P = 1.0$ ), higher diabetes drug costs (\$2,031 vs \$1,522;  $P < 0.001$ ), but similar total healthcare costs (\$14,550 vs \$16,093;  $P = 0.448$ ) and total diabetes-related healthcare costs (\$4,686 vs \$5,604;  $P = 0.416$ ). Short-term disability days and costs were numerically lower in the GLA

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3 cohort (16.0 vs 24.5 days; P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively). Sensitivity  
4 analysis yielded similar findings.  
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8 **Conclusion:**

9 Insulin glargine results in better persistence and adherence, compared with NPH insulin,  
10 with no overall cost disadvantages. Better persistence and adherence may lead to long-term  
11 health benefits for employees with T2DM.  
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For peer review only

## INTRODUCTION

In the United States (US), diabetes affects an estimated 25.8 million people (8.3% of the US population).[1] Type 2 diabetes mellitus (T2DM) and associated comorbidities are associated with disability, reduced productivity, and work loss,[2, 3] which impose an important economic burden on self-insured employers.[4] The diabetes-related economic burden from lost productivity and disability for employees and employers is substantial. Overall, reduced national productivity related to diabetes accounted for \$58 billion in 2007 in the US,[5] while in a more recent study diabetes accounted for 1,473,000 disability-adjusted life years.[6]

A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides clinically relevant improvements in glycemic control with a good safety profile.[7] In addition, early improvements in glucose control can reduce the long-term risk of complications.[8] Options for basal insulin include insulin glargine, a long-acting basal insulin analog, or Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting insulin. Clinical studies have shown that the efficacy of these two agents is similar, but that there is a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, with insulin glargine.[9-11]

Simplicity and convenience of treatment regimens are important for those initiating insulin therapy. Insulin glargine was approved for once-daily injection and may have implications for increased patient persistence and adherence. [12] Although, twice-daily use of insulin glargine might be required to achieve therapeutic goals in some patients with T2DM.[13] Adherence is also associated with improved glycemic control and decreased healthcare resource utilization.[14] and, consequently, may improve outcomes. Other insulin therapy options, such as insulin detemir and insulin lispro protamine suspension, also have convenience and outcomes benefits which may contribute to improved persistence and adherence.[15-17]. In reality, patients taking insulin glargine have been shown to be more likely to persist with their medication than those taking NPH insulin.[18] In general, treatment complexity for chronic conditions – including, though not limited to the need to administer more than one injection daily – correlates with poor adherence.[19]

Adherence to medication also reduces the incidence of complications, and is thus associated with improved work-related outcomes, such as reducing the number of short-term disability days.[20] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[21, 22] People with untreated diabetes, or those with a long duration of the disease, are at increased risk of occupational injury, which is minimized in treated patients

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3 who are adherent to medication.[23] Effective pharmacological management of diabetes with  
4 adequate compliance also results in substantial cost benefits to employers.[21, 24]  
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8 Although there are data in support of the clinical benefits of basal insulins there is currently a  
9 paucity of real-world information about the impact of different basal insulin regimens on  
10 healthcare utilization, employee disability, and their associated costs from **an employer's**  
11 **perspective.**  
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## 14 **METHODS**

### 15 **Database**

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17 This study is a retrospective analysis **from the employer perspective,** of patients' medical  
18 and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters  
19 Database 2003–2009. This database captures person-specific clinical utilization,  
20 expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out  
21 services from about 100 large employers, health plans, and government and public  
22 organizations.  
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29 Short-term disability data were extracted from the MarketScan Health and Productivity  
30 Management Database, which is an integrated database that contains information on  
31 absence, short-term disability, and workers' compensation experience. This information is  
32 linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial  
33 Claims and Encounters Database for these employees, providing a unique and valuable  
34 resource for examining health and productivity issues for an employed, privately insured  
35 population.  
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41 **The MarketScan Research Databases are fully compliant with the letter and spirit of the**  
42 **Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board**  
43 **review was waived.**  
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### 47 **Cohort selection criteria**

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49 Included in the analysis were employees, **but not their dependents,** of 18 years of age or  
50 older with T2DM, defined as having made at least one inpatient visit or two physician visits  
51 dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type  
52 II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th  
53 Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or  
54 unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine  
55 or NPH insulin with the date of the first such claim being the index date **(prescriptions of**  
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3 other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare  
4 benefits and work benefits for short-term disability for 3 months prior to insulin initiation  
5 (baseline period), and 12 months after insulin initiation (follow-up period); and on at least one  
6 oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The  
7 patient cohorts for comparison were determined on the basis of use of insulin glargine or  
8 NPH insulin at initiation of insulin therapy. Outcomes were compared between the matched  
9 cohorts after 1 year of follow-up.  
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### 14 15 **Baseline characteristics**

16 Data were analyzed to assess baseline characteristics, including: gender; age; OAD use;  
17 comorbidities; healthcare utilization/costs; and short-term disability for 3 months prior to  
18 insulin initiation for all patients. Follow-up records were analyzed to assess treatment  
19 persistence, adherence, hypoglycemic events, healthcare resource utilization, cost, and  
20 short-term disability after initiation of insulin therapy.  
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### 25 26 **Persistence and Adherence**

27 Measuring persistence with insulin treatment is challenging due to its non-fixed dose  
28 schedule. Consistent with previously published studies,[25-27] persistence was measured  
29 here as the time the patient had remained on study drugs without discontinuation or  
30 switching following insulin initiation. Study medication was considered discontinued if the  
31 prescription was not refilled within the expected time of medication coverage, defined as the  
32 90th percentile of the time, stratified by the metric quantity supplied, between the first and  
33 second fills among patients with at least one refill. For example, our analysis showed that for  
34 patients who filled prescription for 10 mL and refilled later, 90% of GLA patients refilled it  
35 within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered  
36 discontinuing GLA if he/she previously filled a prescription for 10mL of GLA but did not refill it  
37 within 119 days. Patients who restarted their initial medication after discontinuation, as  
38 defined above, were also considered non-persistent patients. Sensitivity analyses were also  
39 conducted using the 75th and 95th percentiles of the time.  
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48 Treatment adherence was measured during the 1-year follow-up by both the traditional  
49 medication possession ratio (MPR) and the adjusted MPR, which allows for differences in  
50 insulin-device package size [28] (insulin glargine, for example, is packaged either in 10 mL  
51 vials with a total of 1,000 units, or in a 3 mL disposable device in a package of 5 pens with a  
52 total of 1,500 units) to correct the issue that almost all prescriptions are dispensed with a 30-  
53 day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying  
54 the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in  
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3 the analysis period divided by the number of days in the analysis period) by the average  
4 number of days between insulin study drug prescription refills for patients using the insulin  
5 divided by the average days' supply for patients using the insulin. By using data based on  
6 the actual gap between the days' supply and the days to next refill, this adjustment is  
7 necessary to measure real adherent to the instructions from their doctors.  
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### 10 **Clinical outcomes**

11 Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency  
12 department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia  
13 (ICD-9 code 250.8–diabetes with other specified manifestations; 251.0–hypoglycemic coma;  
14 251.1–other specified hypoglycemia; or 251.2–hypoglycemia, unspecified).[29] Daily  
15 average consumption (DACON) of insulin was estimated based on pharmacy claim data and  
16 calculated as the total number of units dispensed before the last refill of study drug divided  
17 by the total number of days between initiation and last refill during follow-up period. A1C  
18 data were not available in this study.  
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### 25 **Healthcare resource utilization and cost**

26 Categories of healthcare resource utilization included numbers of outpatient visits,  
27 emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total  
28 outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare  
29 resource utilization included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx),  
30 and use of anti-hyperglycemic medications, glucose meters and supplies.  
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37 Healthcare costs were computed as paid amounts of adjudicated claims, including insurer  
38 and health-plan payments, copayments and deductibles. Diabetes-specific healthcare costs  
39 included those related to a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx).  
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### 43 **Loss in productivity and its associated costs**

44 Loss in productivity was measured by the total number of days patients were on short-term  
45 disability during the baseline and follow-up periods. The associated costs for short-term  
46 disability were calculated as 70% of \$240 (a figure reflecting the average daily wage paid to  
47 employees of large employers),[30] which amounts to \$168, since disability programs  
48 typically pay for 70% of lost income.[31]  
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### 53 **Total cost**

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3 Total cost was assessed by combining direct costs (healthcare) and indirect costs (short-  
4 term disability costs), and comparisons between groups were made. Costs were adjusted for  
5 inflation to 2010 US dollars using the medical care component of the Consumer Price Index.  
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### 8 9 **Statistical analyses**

10 To reduce the observed baseline selection bias, such as confounding by indication,  
11 between the two study cohorts, propensity score matching (PSM) methodology [32] was  
12 implemented, with a stringent 2:1 matching of patients initiating insulin glargine or NPH  
13 insulin. Propensity scores for initiating insulin glargine vs NPH were calculated from a logistic  
14 regression model that estimated the likelihood of initiating insulin glargine based on the  
15 observed patient characteristics. Covariates were selected based on their hypothesized  
16 confounding relationship with the outcome variables, and included age, gender, region,  
17 health plan type, Charlson Comorbidity Index, and baseline concomitant medications,  
18 hypoglycemic events, healthcare utilization (overall or disease-related), co-pays, and  
19 healthcare cost (overall or disease-related). Sensitivity analyses were also conducted using  
20 1:1 and 3:1 PSM.  
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29 Among the matched cohorts, all study variables, including baseline and outcome measures,  
30 were analyzed descriptively. Results were stratified by treatment cohort. For dichotomous  
31 variables, P values were calculated according to the Mann–Whitney U test; for continuous  
32 variables, t tests were used to calculate P values. P values of <0.05 were taken to be  
33 indicative of a significant difference. Kaplan–Meier survival curve and the log-rank test were  
34 used to compare 1-year treatment persistence. The relationship between hospitalization and  
35 short-term disability was investigated by the chi-squared test and Pearson's correlation  
36 analysis.  
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## 42 **RESULTS**

### 43 **Baseline characteristics**

44 Data from 2,454 patient records were eligible for the 1-year follow-up analyses: 2,250 in the  
45 insulin glargine (GLA) cohort, and 204 in the NPH insulin (NPH) cohort. Before the matching,  
46 GLA patients were more likely to be male, older, using insulin pen, and had higher  
47 copayment than NPH patients (data not shown here), indicating confounding by indication as  
48 selection bias. The 2:1 PSM yielded a total of 534 patients (GLA: 356; NPH 178) with well-  
49 matched baseline characteristics (table 1). Overall, 43.8% of the patients included in the  
50 analysis were women; mean age was 49 years (range: 20–64 years), and the mean number  
51 of OADs was 1.8. The baseline hospitalization rate was 15.2%, with a mean short-term  
52 disability of 3.0 days.  
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**Table 1.** Baseline characteristics (3 months prior to index)

	<b>Insulin glargine (n=356)</b>	<b>NPH insulin (n=178)</b>	<b>P value</b>
Gender, female (%)	153 (42.9%)	81 (45.5%)	0.5789
Age, years, mean ± SD	49 ± 10	49 ± 10	0.7580
	18–39, n (%)	35 (19.6%)	0.5988
	40–64, n (%)	143 (80.3%)	0.5988
Health plan, n (%)			0.9390
	CDHP	5 (1.4%)	2 (1.1%)
	Comprehensive	34 (9.5%)	18 (10.1%)
	HMO	63 (17.6%)	36 (20.2%)
	POS	65 (18.2%)	29 (16.2%)
	PPO	189 (53.0%)	93 (52.2%)
Region, n (%)			
	North Central Region	82 (23.0%)	45 (25.2%)
	Northeast Region	58 (16.2%)	32 (17.9%)
	South Region	129 (36.2%)	54 (30.3%)
	West Region	85 (23.8%)	45 (25.2%)
	Unknown	2 (0.5%)	2 (1.1%)
Insulin Pen use, n (%)	59 (16.5%)	33 (18.5%)	
Antidiabetic drugs, n (%)			
	Metformin	262 (73.5%)	132 (74.1%)
	Sulfonylureas	223 (62.6%)	105 (58.9%)
	Thiazolidinediones	133 (37.3%)	68 (38.2%)
	DPP-4 inhibitors	9 (2.5%)	6 (3.3%)
	Exenatide	30 (8.4%)	11 (6.1%)
Number of OADs, mean ± SD	1.81 ± 0.73	1.80 ± 0.75	0.9015
Charlson Comorbidity Index, mean ± SD	0.284 ± 0.819	0.281 ± 1.159	0.9770
Comorbidities, n (%)			
	Obesity	5 (1.4)	4 (2.2)
	Hypertension	76 (21.3)	39 (21.9)
	Hyperlipidemia	39 (10.9)	22 (12.3)
	Congestive heart failure	12 (3.3)	4 (2.2)
	Retinopathy	7 (1.9)	5 (2.8)
	Neuropathy	19 (5.3)	8 (4.4)
	Nephropathy	15 (4.2)	3 (1.6)
Total healthcare utilization, n (%) or mean ± SD [median]			
	Hospitalizations	53 (14.8%)	28 (15.7%)
	Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]
	ER visits	80 (22.4%)	38 (21.3%)
	Endocrinologist visits	38 (10.6%)	25 (14.0%)
	Hospitalization/patient	0.16 ± 0.39 [0]	0.17 ± 0.42 [0]
	ER visits/patient	0.31 ± 0.67 [0]	0.28 ± 0.68 [0]
	Endocrinologist visits/patient	0.15 ± 0.48 [0]	0.19 ± 0.55 [0]
Diabetes-related healthcare utilization, n (%) or mean ± SD [median]			
	Hospitalizations	34 (9.5%)	20 (11.2%)
	ER visits	37 (10.3%)	17 (9.5%)
	Endocrinologist visits	36 (10.1%)	23 (12.9%)
	Office visits	297 (83.4%)	138 (77.5%)
	Hospitalizations/patient	0.10 ± 0.29	0.11 ± 0.32
	ER visits/patient	0.13 ± 0.40 [0]	0.11 ± 0.34 [0]
	Endocrinologist visits/patient	0.14 ± 0.47 [0]	0.17 ± 0.53 [0]
	Office visits/patient	1.74 ± 1.43 [1]	1.60 ± 1.44 [1]
	Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean ± SD [median]			
	Inpatient cost	2756 ± 12393 [0]	1958 ± 8241 [0]
	Outpatient cost	1385 ± 3652 [498]	1766 ± 4243 [613]
	ER cost	181 ± 476 [0]	144 ± 515 [0]
	Prescription cost	937 ± 1236 [677]	926 ± 1065 [699]

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Total cost	5259 ± 14237 [1632]	4794 ± 10731 [1895]	0.6735
Total diabetes-related healthcare cost, mean ± SD [median]			
Inpatient cost	1304 ± 6588 [0]	811 ± 3447 [0]	0.2570
Outpatient cost	242 ± 321 [158]	274 ± 505 [131]	0.4393
ER cost	46 ± 216 [0]	34 ± 195 [0]	0.5346
Prescription cost	294 ± 293 [204]	285 ± 309 [154]	0.7474
Supply cost	48 ± 97 [0]	46 ± 92 [0]	0.7766
Total cost	1934 ± 6551 [621]	1450 ± 3485 [596]	0.2658
Co-pay, n (%)			
\$0–\$15	166 (46.6%)	87 (48.8%)	0.8694
\$15–\$30	147 (41.2%)	71 (39.8%)	
\$30+	42 (11.7%)	20 (11.2%)	
Unknown	1 (0.2%)	0 (0.0%)	
Short-term disability, mean ± SD			
Occurrence count	0.12 ± 0.34	0.12 ± 0.37	0.9310
Days	3.10 ± 12.97	2.98 ± 12.9	0.9153
Cost	538 ± 2250	534 ± 2349	0.9856
Total cost (healthcare + short-term disability), mean ± SD	5797 ± 15005	5328 ± 12174	0.6987

Baseline information is collected within 3 months prior to index date. CDHP, consumer-driven health plan; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; ER, Emergency Room; HMO, health maintenance organization; NPH, neutral protamine Hagedorn insulin; OADs, oral antidiabetic drugs; POS point of service; PPO, preferred provider organization; SD, standard deviation.

### Persistence and adherence

During the 1-year follow-up, patients receiving insulin glargine were significantly more persistent (table 2, figure 1) and adherent compared with those in the NPH insulin cohort (table 2). Over half (54.5%) of patients on insulin glargine were persistent, compared with 43.8% of those on NPH (P=0.0225). Patients stayed on insulin glargine treatment for a significantly longer period (approximately 22 days longer) than those on NPH insulin (284 vs 262 days, P=0.0178). The Kaplan–Meier survival curve shows that patients treated with NPH discontinued sooner than those treated with insulin glargine (log-rank test P-value=0.0073; figure 2). Sensitivity analyses using the 75th and 95th percentiles yielded similar results, with all indicating better persistence with insulin glargine compared with NPH insulin (75th percentile: 34.0% vs 28.1%, P=0.17; 95th percentile: 67.2% vs 57.9%, P=0.039). Both traditional and adjusted MPR values indicated a significantly better adherence to treatment with insulin glargine, compared with NPH insulin (table 2, figure 1).

**Table 2. Follow-up treatment persistence, hypoglycemia, healthcare utilization and loss in productivity**

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Persistence/adherence, n (%) or mean ± SD			
Treatment persistence	186 (54.5)	75 (43.8)	0.0225

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Treatment persistence days	283.85 ± 96.92	261.77 ± 103.35	0.0178
MPR,	0.50 ± 0.28	0.45 ± 0.30	0.0418
Adjusted MPR	0.67 ± 0.33	0.61 ± 0.35	0.0380
DACON	30.6 ± 21.1	35.8 ± 31.9	0.0740
<b>Hypoglycemia, n (%) or mean ± SD</b>			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
<b>Total healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	82 (23%)	56 (31.4%)	0.0360
ER visits	104 (29.2%)	57 (32.0%)	0.5049
Endocrinologist visits	68 (19.1%)	48 (26.9%)	0.0377
Office visits	352 (98.8%)	177 (99.4%)	0.5251
Hospitalizations/patient	0.28 ± 0.58 [0]	0.41 ± 0.73 [0]	0.0353
ER visits/patient	0.56 ± 1.43 [0]	0.54 ± 1.03 [0]	0.8353
Endocrinologist visits/patient	0.61 ± 1.57 [0]	0.94 ± 1.84 [0]	0.0422
Office visits/patient	18.37 ± 17.43 [14]	18.30 ± 14.98 [14]	0.9615
Total hospitalization days	1.29 ± 4.54 [0]	2.06 ± 4.98 [0]	0.0754
<b>Diabetes-related healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	45 (12.6%)	27 (15.1%)	0.4201
ER visits	43 (12.0%)	27 (15.1%)	0.3186
Endocrinologist visits	68 (19.1%)	45 (25.2%)	0.0993
Office visits	341 (95.7%)	168 (94.3%)	0.4689
Hospitalizations/patient	0.14 ± 0.38 [0]	0.15 ± 0.36 [0]	0.6801
ER visits/patient	0.20 ± 0.81 [0]	0.16 ± 0.40 [0]	0.5207
Endocrinologist visits/patient	0.56 ± 1.45 [0]	0.80 ± 1.65 [0]	0.1100
Office visits/patient	5.69 ± 3.98 [5]	5.56 ± 4.23 [5]	0.7293
Total hospitalization days	0.56 ± 2.50 [0]	0.53 ± 1.99 [0]	0.8659
<b>Loss in productivity, mean ± SD</b>			
Short-term disability occurrences	0.36 ± 0.70	0.38 (0.70)	0.7944
Short-term disability days	15.96 ± 38.78	24.51 ± 60.33	0.0862

DACON, daily average consumption; ER, Emergency Room; NPH, neutral protamine Hagedorn insulin; SD, standard deviation

### Clinical outcomes

Clinical outcomes of the two agents were similar, both in terms of hypoglycemia-related event rates (both cohorts had overall hypoglycemia rates of 4.4%; P=1.0) and DACON (insulin glargine: 30.6 units vs NPH insulin: 35.8 units, P=0.074) (table 2).

### Healthcare utilization and cost

In terms of total healthcare utilization and cost, patients in the insulin glargine cohort also had lower rates of hospitalization, compared with those in the NPH insulin cohort (23.0% vs 31.4%; P=0.036, respectively; table 2), and of endocrinologist visits (19.1% vs 26.9%; P=0.038), despite similar utilization at baseline (table 1). All diabetes-related healthcare utilization outcomes were similar between the cohorts (table 2). With respect to cost outcomes, the total overall healthcare costs were similar for the insulin glargine and NPH insulin cohorts (\$14,550 vs \$16,093, respectively; P=0.448), as were total diabetes-related healthcare costs (\$4,686 vs \$5,604; P=0.416) (figure 3). Similar total diabetes-related healthcare costs were reported despite significantly higher diabetes-related prescription

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3 costs for the insulin glargine cohort (\$2,031), compared with the NPH insulin cohort (\$1,522)  
4 (P<0.001).  
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### 7 **Loss in productivity and its associated costs**

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9 In terms of loss in productivity and the associated costs for employers, the incidence of  
10 claims for short-term disability was 0.36 per patient per year in the insulin glargine group,  
11 compared with 0.38 in the NPH insulin group (P=0.7944). However, the total number of  
12 short-term disability days and the associated cost were numerically lower in the insulin  
13 glargine group (16.0 vs 24.5 days; P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively.  
14 figure 3). Combined total costs were similar between the insulins (\$17,374 for GLA vs  
15 \$20,455 for NPH, P=0.204).  
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### 20 **Correlations**

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22 In the 2:1 matched cohorts, the chi-squared tests showed that patients who were not  
23 persistent with their insulin treatment were significantly more likely to have a claim for short-  
24 term disability (33.47% vs. 22.22%, P=0.0045), and so were those with hospitalizations  
25 (60.1% vs. 15.7%, P <0.001). **Pearson's correlation test showed that higher number of**  
26 **insulin persistence days was correlated with lower number of short-term-disability days (r=-**  
27 **0.1325, P=0.0027), while higher number of hospitalizations was correlated with higher**  
28 **number of short-term disability claims (r=0.40, P<0.0001).**  
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### 39 **Sensitivity analysis**

40 The sensitivity analyses using 1:1 and 3:1 PSM yielded similar results overall. In the 1:1  
41 PSM analysis (n=199, both cohorts), persistence with treatment was higher with insulin  
42 glargine than with NPH insulin (75th percentile: 32.8% vs 26.0%, P=0.146; 90th percentile:  
43 51.0% vs 41.1%, P=0.052; 95th percentile: 66.1% vs 54.6%, P=0.022). Treatment adherence  
44 was also higher with insulin glargine than with NPH insulin (MPR: 0.49 vs 0.43, P=0.039;  
45 adjusted MPR: 0.66 vs 0.60; P=0.070). A significantly lower hospitalization rate (26.1% vs  
46 36.1%, P=0.030), lower endocrinologist visit rate (17.0% vs 26.1%, P=0.028), fewer  
47 hospitalization days (1.32 vs 2.29 days, P=0.026), fewer short-term disability days and lower  
48 associated costs (12.33 days vs 27.67 days; P=0.002 and \$2,173 vs \$4,942; P=0.002,  
49 respectively) were reported with insulin glargine than with NPH insulin in the 1:1 PSM  
50 analysis. Total costs in the 1:1 matched cohort were also significantly lower in the GLA  
51 cohort than in the NPH cohort (\$15,720 vs \$21,398, P=0.022). The results from the 3:1 PSM  
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3 analysis (n=480, insulin glargine; n=160, NPH insulin) were consistent with those from the  
4 2:1 PSM analysis.  
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## 7 DISCUSSION

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9 In this real-world study, use of insulin glargine was associated with better persistence and  
10 adherence than NPH insulin. In addition, a lower healthcare resource utilization was  
11 associated with insulin glargine than NPH insulin, in terms of hospitalizations and  
12 endocrinologist visits, over 1 year of follow-up. Rates of hypoglycemia-related events were  
13 similar with the two treatments. Furthermore, diabetes drug-related costs were higher with  
14 insulin glargine than with NPH insulin, likely due to higher drug price of insulin glargine, and  
15 also the improved persistence/adherence associated with it. However, both total diabetes-  
16 related and total healthcare costs were similar in the two groups, as a consequence of the  
17 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated  
18 with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations  
19 and endocrinologist visits were also numerically lower in GLA group but not statistically  
20 significant, probably due to sample size and the inaccuracy of using ICD-9-CM diagnosis  
21 code (250.xx) to capture diabetes-related events. In regard to short-term disability in both  
22 primary and sensitivity analyses, numerically fewer short-term disability days and lower  
23 associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort,  
24 but this was not significant. It is likely that the reduction in short-term disability is related to  
25 fewer hospitalizations in the insulin glargine cohort. Indeed, the correlation analysis showed  
26 that patients with any hospitalizations were significantly more likely to claim for short-term  
27 disability: both the number and duration of hospitalizations were highly correlated with the  
28 number of claims and the duration of short-term disability.  
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41 A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in  
42 patients with T2DM have indicated that insulin glargine represents an economic treatment  
43 option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at  
44 least as effective glycemic control as NPH insulin, and to be cost effective in a range of  
45 countries and settings.[33-39]  
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49 Basal insulin analogs have been shown to have several advantages compared to NPH  
50 insulin including less pharmacologic variability, lower risk of hypoglycemia, and greater  
51 impact on quality of life.[14-16, 40] The rates of hypoglycemia-related events were, however,  
52 similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated  
53 with less hypoglycemia than NPH insulin,[15] the switch from NPH insulin to insulin glargine  
54 may usually be considered in patients with evidence of hypoglycemia or increasing incidence  
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3 of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this  
4 study were similar, and thus it is possible that the NPH insulin cohort in the present analysis  
5 may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.  
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9 The increased persistence associated with insulin glargine, as shown in this study, may lead  
10 to better clinical outcomes,[41] and potentially improve work-related outcomes.[13, 20, 23]  
11 Diabetes-related disability has been shown to result in loss of work place productivity.[42-46]  
12 In this study, we observed fewer short-term disability days in patients on insulin glargine,  
13 compared with those on NPH insulin. Although the differences were not statistically  
14 significant, this finding may suggest that initiation of therapy with insulin glargine could help  
15 increase workplace productivity among employed patients with T2DM compared with those  
16 initiating with NPH insulin.  
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23 As with all retrospective studies, issues of sampling bias should be taken into account when  
24 interpreting these results, which may introduce selection bias. The use of PSM methodology  
25 in this study should have helped reduce the impact of selection bias such as confounding by  
26 indication. In fact, three different matching ratios were tested, and all yielded similar findings.  
27 However, it likely limited patients in the insulin glargine cohort to those most similar to the  
28 NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further,  
29 some insulin patients may have been missed due to the availability of 90 day/mail order  
30 prescriptions resulting in them being missed during the 3 month baseline period.  
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37 This study has several limitations. Although the MarketScan data represent a large diverse  
38 population, it only included information from mainly large, self-insured employers, whose  
39 employees were more likely to locate in certain geographic areas than the general employee  
40 population, and the analysis included a convenience sample of patients whose employer  
41 supplied productivity data. Therefore, this study should not be assumed as representative of  
42 the overall US population. As any retrospective observational study, causality of treatment  
43 effects cannot be established in this study. Although the propensity score matching method  
44 was used to reduce the treatment selection bias issues such as confounding by indications,  
45 it also led to significant reduction in the sample size, particularly on the GLA group, due to  
46 the required matching ratios, and relatively much smaller sample size in NPH group. This  
47 may also makes the study underpowered to detect all significant differences between  
48 treatment groups. In addition, the similar rate of hypoglycemia observed between groups is  
49 inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia  
50 with insulin glargine, compared with NPH insulin.[9, 33] It is unlikely that rates of  
51 hypoglycemia would be captured with the same level of sensitivity in this retrospective  
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3 analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia  
4 rate in both cohorts may have resulted in insufficient statistical power to detect significant  
5 differences. Coding issues in the claim data may also have contributed to the lack of  
6 statistical robustness. The daily units of insulin (DACON) was measured based on pharmacy  
7 claim data and may not be accurate. For example, patients on a low dose are instructed to  
8 discard unused insulin (particularly in vials) after approximately 1 month, pharmacy claim  
9 data can lead to an overestimation of DACON. However, this is unlikely to affect GLA and  
10 NPH groups disproportionately because they were similar in proportion of patients using  
11 insulin pen. (Table 2) A1C data were not available, so neither the effectiveness of glycemic  
12 control nor the association with hypoglycemia could be assessed. Finally, the 12 month  
13 follow-up period of this study may not have been sufficient to detect benefits due to improved  
14 persistence and adherence.  
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## 22 CONCLUSION

23 This study showed that insulin glargine resulted in better persistence and adherence, with  
24 lower health care utilization, at similar total healthcare costs despite higher drug-related  
25 costs, than NPH insulin. Better persistence and adherence may lead to long-term health  
26 benefits and additional benefits to patients with T2DM and their employers. Due to the  
27 retrospective nature of this study, further studies need to be conducted to confirm these  
28 findings.  
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## 41 DISCLOSURES

42 LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis  
43 U.S.  
44

45 RM and WW: Employees of sanofi-aventis U.S.  
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49

## 50 CONTRIBUTIONS

51 LW: Active in study design, statistical plan, data analysis, drafting, and review of manuscript.  
52

53 WW: Active in creating the concept and study design, drafting, and review of manuscript.  
54

55 RM: Active in creating the concept and study design, drafting, and review of manuscript.  
56

57 LX: Role in statistical analysis and review of manuscript.  
58

59 OB: Active in creating the study design, statistical plan, and review of manuscript.  
60

**DATA SHARING**

Additional data is available by e-mailing Dr Onur Baser [obaser@statinmed.com](mailto:obaser@statinmed.com)

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3 **Figure legends**

4 **Figure 1** Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

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7 \*P<0.05 vs insulin glargine

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11 **Figure 2** Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine  
12 and NPH insulin

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17 **Figure 3** 1-year short-term disability and direct healthcare costs. (Total between-group  
18 differences did not reach statistical significance).

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**Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study**

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**Title:**

Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study

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## Article Summary

### Article Focus

- Do differences seen in the outcomes of randomized controlled trials comparing insulin glargine and neutral protamine Hagedorn (NPH) translate to improved real-world outcomes in employed adults living in the United States?

### Key Messages

- Insulin glargine was associated with better persistence, lower inpatient admission, which offset its higher drug cost, and lower indirect costs from short-term disability, than NPH insulin.
- Reduced short-term disability and improved adherence with insulin glargine may improve long-term productivity, compared with NPH insulin, and provide benefits to both employees and their employers.

### Strengths and Limitations

- *Strengths*
  - The MarketScan database represents a large and diverse data source.
  - The database captures detailed information on both employees' healthcare resource utilization and their productivity, as measured by short-term disability.
  - The use of propensity-score-matching methodology reduces treatment selection bias between insulin glargine and NPH groups.
  - Sensitivity analysis confirmed the consistency of findings.
- *Limitations:*
  - As with all retrospective studies, causality of treatment effects cannot be established in this study. This study used a convenience sample, so it is not representative of the overall US population, and also may be underpowered to detect all significant differences between groups.
  - Confounding by indication or prognosis may be sources of bias in this retrospective observational study.
  - It is unlikely that rates of hypoglycemia and other clinical outcomes would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, A1C data were not available, so neither the effectiveness of glycemic control nor its association with hypoglycemia could be assessed.

**[Abstract]****Limit: 300 words****Current: 299 words**

**Objectives:** To compare real-world outcomes of initiating insulin glargine (GLA) versus neutral protamine Hagedorn (NPH) insulin among employees with type 2 diabetes mellitus (T2DM) who had both employer-sponsored health insurance and short-term-disability coverages.

**Design:** Retrospective cohort study

**Setting:** MarketScan Commercial Claims and Encounters/Health and Productivity Management Databases 2003–2009.

**Participants:** Adult employees with T2DM who were previously treated with oral antidiabetic drugs and/or glucagon-like-peptide 1 receptor agonists, and initiated GLA or NPH were included if they were continuously enrolled in healthcare and short-term-disability coverages for 3 months before (baseline) and 1 year after (follow-up) initiation. Treatment selection bias was addressed by 2:1 propensity score matching. Sensitivity analyses were conducted using different matching ratios.

**Primary and secondary outcome measures:** Outcomes during 1-year follow-up were measured and compared: insulin treatment persistence and adherence; hypoglycemia rates and daily average consumption of insulin; total and diabetes-specific healthcare resource utilization and costs; and loss in productivity, as measured by short-term disability, and the associated costs.

**Results:** A total of 534 patients were matched and analyzed (GLA: 356; NPH 178) with no significant differences in baseline characteristics. GLA patients were more persistent and adherent (both  $P < 0.05$ ), had lower rates of hospitalization (23.0% vs 31.4%;  $P = 0.036$ ) and endocrinologist visits (19.1% vs 26.9%;  $P = 0.038$ ), similar hypoglycemia rates (both 4.4%;  $P = 1.0$ ), higher diabetes drug costs (\$2,031 vs \$1,522;  $P < 0.001$ ), but similar total healthcare costs (\$14,550 vs \$16,093;  $P = 0.448$ ) and total diabetes-related healthcare costs (\$4,686 vs \$5,604;  $P = 0.416$ ). Short-term disability days and costs were numerically lower in the GLA cohort (16.0 vs 24.5 days;  $P = 0.086$  and \$2,824 vs \$4,363;  $P = 0.081$ , respectively). Sensitivity analyses yielded similar findings.

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3 **Conclusion:** Insulin glargine results in better persistence and adherence, compared with  
4 NPH insulin, with no overall cost disadvantages. Better persistence and adherence may lead  
5 to long-term health benefits for employees with T2DM.  
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For peer review only

## INTRODUCTION

In the United States (US), diabetes affects an estimated 25.8 million people (8.3% of the US population).[1] Type 2 diabetes mellitus (T2DM) and associated comorbidities are associated with disability, reduced productivity, and work loss,[2, 3] which impose an important economic burden on self-insured employers.[4] The diabetes-related economic burden from lost productivity and disability for employees and employers is substantial. Overall, reduced national productivity related to diabetes accounted for \$58 billion in 2007 in the US,[5] while in a more recent study diabetes accounted for 1,473,000 disability-adjusted life years.[6]

Early improvements in glucose control can reduce the long-term risk of complications associated with T2DM.[7] Adherence to anti-hyperglycemic interventions is also associated with improved glycemic control and decreased healthcare resource utilization[8] and, consequently, may improve outcomes. Adherence to medication also reduces the incidence of complications, and is thus associated with improved work-related outcomes, such as reducing the number of short-term disability days.[9] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[10, 11] People with untreated diabetes, or those with a long duration of the disease, are at increased risk of occupational injury, which is minimized in treated patients who are adherent to medication.[12] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[10, 13]

A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides clinically relevant improvements in glycemic control with a good safety profile.[14] Options for basal insulin include insulin glargine, a long-acting basal insulin analog, or neutral protamine Hagedorn (NPH) insulin, an intermediate-acting insulin. Clinical studies have shown that the efficacy of these two agents is similar, but that there is a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, with insulin glargine.[15-17]

Simplicity and convenience of treatment regimens are important for those initiating insulin therapy. Insulin glargine was approved for once-daily injection and may have implications for increased patient persistence and adherence.[18] However, twice-daily use of insulin glargine might be required to achieve therapeutic goals in some patients with T2DM.[19] Other insulin therapy options, such as insulin detemir and insulin lispro protamine suspension, also have convenience and outcomes benefits which may contribute to improved persistence and adherence.[20-22]. In reality, patients taking insulin glargine have been shown to be more likely to persist with their medication than those taking NPH

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3 insulin.[23] In general, treatment complexity for chronic conditions – including, though not  
4 limited to the need to administer more than one injection daily – correlates with poor  
5 adherence.[24]  
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9 Although there are data in support of the clinical benefits of basal insulins, there is currently  
10 a paucity of real-world information about the impact of different basal insulin regimens on  
11 healthcare utilization, employee disability, and their associated costs from an employer's  
12 perspective. This analysis was performed in order to compare real-world outcomes from  
13 initiating insulin glargine or NPH insulin among employees with T2DM who had both  
14 employer-sponsored health insurance and short-term-disability coverages. As insulin detemir,  
15 another long-acting basal insulin analog, was only launched in the US in 2006, too few  
16 patients were being treated with this agent for it to be included in the analysis as a  
17 comparator.  
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## 26 **METHODS**

### 27 **Database**

28 This study is a retrospective analysis from the employer perspective of patients' medical and  
29 pharmacy claims extracted from the MarketScan Commercial Claims and Encounters  
30 Database 2003–2009. This database captures person-specific clinical utilization,  
31 expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out  
32 services from about 100 large employers, health plans, and government and public  
33 organizations.  
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39 Short-term disability data were extracted from the MarketScan Health and Productivity  
40 Management Database, which is an integrated database that contains information on  
41 absence, short-term disability, and workers' compensation experience. This information is  
42 linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial  
43 Claims and Encounters Database for these employees, providing a unique and valuable  
44 resource for examining health and productivity issues for an employed, privately insured  
45 population.  
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51 The MarketScan Research Databases are fully compliant with the letter and spirit of the  
52 Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board  
53 review was waived.  
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### 58 **Cohort selection criteria**

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3 Included in the analysis were employees, but not their dependents, of 18 years of age or  
4 older with T2DM, defined as having made at least one inpatient visit or two physician visits  
5 dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type  
6 II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th  
7 Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or  
8 unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine  
9 or NPH insulin with the date of the first such claim being the index date (prescriptions of  
10 other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare  
11 benefits and work benefits for short-term disability for 3 months prior to insulin initiation  
12 (baseline period) and 12 months after insulin initiation (follow-up period); and on at least one  
13 oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The  
14 patient cohorts for comparison were determined on the basis of use of insulin glargine or  
15 NPH insulin at initiation of insulin therapy. Patients initiating insulin detemir were excluded  
16 from the current study because it was only available after 2006, and thus an insufficient  
17 number of patients (fewer than 100) was identified in the database to provide adequate  
18 statistical power for meaningful comparisons. Outcomes were compared between the  
19 matched cohorts after 1 year of follow-up.  
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### 30 **Baseline characteristics**

31 Data were analyzed to assess baseline characteristics, including: gender, age, OAD use,  
32 comorbidities, healthcare utilization/costs, index drug co-pay, and short-term disability for 3  
33 months prior to insulin initiation for all patients. Follow-up records were analyzed to assess  
34 treatment persistence, adherence, hypoglycemic events, healthcare resource utilization,  
35 cost, and short-term disability after initiation of insulin therapy.  
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### 41 **Persistence and Adherence**

42 Measuring persistence with insulin treatment is challenging due to its non-fixed dose  
43 schedule. Consistent with previously published studies,<sup>[25-27]</sup> persistence was measured  
44 here as the time the patient had remained on study drug without discontinuation or switching  
45 following insulin initiation. Study medication was considered discontinued if the prescription  
46 was not refilled within the expected time of medication coverage, defined as the 90th  
47 percentile of the time, stratified by the metric quantity supplied, between the first and second  
48 fills among patients with at least one refill. For example, our analysis showed that for  
49 patients who filled a prescription for 10 mL and refilled later, 90% of insulin glargine patients  
50 refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient was  
51 considered to have discontinued insulin glargine if he/she previously filled a prescription for  
52 10mL of insulin glargine but did not refill it within 119 days. Patients who restarted their initial  
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3 medication after discontinuation, as defined above, were also considered non-persistent  
4 patients. Sensitivity analyses were also conducted using the 75th and 95th percentiles of the  
5 time.  
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9 Treatment adherence was measured during the 1-year follow-up by both the traditional  
10 medication possession ratio (MPR) and the adjusted MPR, which allows for differences in  
11 insulin-device package size [28] (insulin glargine, for example, is packaged either in 10 mL  
12 vials with a total of 1,000 units or in a 3 mL disposable device in a package of 5 pens with a  
13 total of 1,500 units) to correct the issue that almost all prescriptions are dispensed with a 30-  
14 day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying  
15 the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in  
16 the analysis period divided by the number of days in the analysis period) by the average  
17 number of days between insulin study drug prescription refills for patients using the insulin  
18 divided by the average days' supply for patients using the insulin. By using data based on  
19 the actual gap between the days' supply and the days to next refill, this adjustment is  
20 necessary to measure real adherence to doctor's instructions.  
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### 28 29 **Clinical outcomes**

30 Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency  
31 department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia  
32 (ICD-9 code 250.8–diabetes with other specified manifestations; 251.0–hypoglycemic coma;  
33 251.1–other specified hypoglycemia; or 251.2–hypoglycemia, unspecified).[29] Daily  
34 average consumption (DACON) of insulin was estimated based on pharmacy claims data  
35 and calculated as the total number of units dispensed before the last refill of study drug  
36 divided by the total number of days between initiation and last refill during follow-up period.  
37 Glycated hemoglobin (A1C) data were not available in this study.  
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### 45 **Healthcare resource utilization and cost**

46 Categories of healthcare resource utilization included numbers of outpatient visits,  
47 emergency room (ER) visits, inpatient admissions, inpatient length of stay (days), and total  
48 outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare  
49 resource utilization included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx),  
50 and use of anti-hyperglycemic medications, glucose meters, and supplies.  
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3 Healthcare costs were computed as paid amounts of adjudicated claims, including insurer  
4 and health-plan payments, copayments, and deductibles. Diabetes-specific healthcare costs  
5 included those related to a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx).  
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### 8 9 **Loss in productivity and its associated costs**

10 Loss in productivity was measured by the total number of days patients were on short-term  
11 disability during the baseline and follow-up periods. The associated costs for short-term  
12 disability were calculated as 70% of \$240 (a figure reflecting the average daily wage paid to  
13 employees of large employers),[30] which amounts to \$168, since disability programs  
14 typically pay for 70% of lost income.[31]  
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### 18 19 **Total cost**

20 Total cost was assessed by combining direct costs (healthcare costs) and indirect costs  
21 (short-term disability costs), and comparisons between groups were made. Costs were  
22 adjusted for inflation to 2010 US dollars using the medical care component of the Consumer  
23 Price Index.  
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### 28 29 **Statistical analyses**

30 To reduce the observed baseline selection bias between the two study cohorts, propensity  
31 score matching (PSM) methodology [32] was implemented, with a stringent 2:1 matching of  
32 patients initiating insulin glargine or NPH insulin. Propensity scores for initiating insulin  
33 glargine versus NPH were calculated from a logistic regression model that estimated the  
34 likelihood of initiating insulin glargine based on the observed patient characteristics.  
35 Covariates were selected based on their hypothesized confounding relationship with the  
36 outcome variables, and included age, gender, region, health plan type, Charlson  
37 Comorbidity Index, and baseline concomitant medications, hypoglycemic events, healthcare  
38 utilization (overall or disease-related), co-pays, and healthcare cost (overall or disease-  
39 related). Sensitivity analyses were also conducted using 1:1 and 3:1 PSM.  
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47 Among the matched cohorts, all study variables, including baseline and outcome measures,  
48 were analyzed descriptively. Results were stratified by treatment cohort. For dichotomous  
49 variables, P values were calculated according to the Mann–Whitney U test; for continuous  
50 variables, t tests were used to calculate P values. Kaplan–Meier survival curves and the log-  
51 rank test were used to compare 1-year treatment persistence. Relationships between  
52 treatment persistence and hospitalization as well as short-term disability were investigated  
53 by the chi-squared test. P values of <0.05 were taken to be indicative of a significant  
54 difference.  
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## RESULTS

### Baseline characteristics

Data from 2,454 patient records were eligible for the 1-year follow-up analyses: 2,250 in the insulin glargine cohort, and 204 in the NPH insulin cohort. Before the matching, patients using insulin glargine were more likely to be male, older, using insulin pen, and have higher copayment than those using NPH (data not shown here). The 2:1 PSM yielded a total of 534 patients (insulin glargine, n=356; NPH insulin, n=178) with well-matched baseline characteristics (table 1).

**Table 1.** Baseline characteristics (3 months prior to index)

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Gender, female (%)	153 (42.9%)	81 (45.5%)	0.5789
Age, years, mean $\pm$ SD	49 $\pm$ 10	49 $\pm$ 10	0.7580
Health plan, n (%)			0.9390
	CDHP	2 (1.1%)	
	Comprehensive	18 (10.1%)	
	HMO	36 (20.2%)	
	POS	29 (16.2%)	
	PPO	93 (52.2%)	
Region, n (%)			
	North Central Region	45 (25.2%)	0.5653
	Northeast Region	32 (17.9%)	0.6238
	South Region	54 (30.3%)	0.1758
	West Region	45 (25.2%)	0.7215
	Unknown	2 (1.1%)	0.4778
Pen use for Initiated Insulin, n (%)	59 (16.5%)	33 (18.5%)	0.5706
Antidiabetic drugs, n (%)			
	Metformin	132 (74.1%)	0.8893
	Sulfonylureas	105 (58.9%)	0.4138
	Thiazolidinediones	68 (38.2%)	0.8497
	DPP-4 inhibitors	6 (3.3%)	0.5785
	Exenatide	11 (6.1%)	0.3579
Number of OADs, mean $\pm$ SD	1.81 $\pm$ 0.73	1.80 $\pm$ 0.75	0.9015
Charlson Comorbidity Index, mean $\pm$ SD	0.284 $\pm$ 0.819	0.281 $\pm$ 1.159	0.9770
Comorbidities, n (%)			
	Hypertension	39 (21.9)	0.8817
	Hyperlipidemia	22 (12.3)	0.6305
	Retinopathy	5 (2.8)	0.5357
	Neuropathy	8 (4.4)	0.6752
	Nephropathy	3 (1.6)	0.1270
Healthcare utilization, n (%) or mean $\pm$ SD [median]			
	All-cause Hospitalizations	28 (15.7%)	0.7980
	All-cause Total hospitalization days	0.97 $\pm$ 3.38 [0]	0.72 $\pm$ 2.11 [0]
	All-cause ER visits	38 (21.3%)	0.7680
	Endocrinologist visits	25 (14.0%)	0.2550
	Diabetes-related Hospitalizations	20 (11.2%)	0.5426
	Diabetes-related Total hospitalization days	0.52 $\pm$ 2.31 [0]	0.41 $\pm$ 1.49 [0]
	Diabetes-related ER visits	17 (9.5%)	0.7608
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean $\pm$ SD [median]			

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Inpatient cost	2756 ± 12393 [0]	1958 ± 8241 [0]	0.3766
Outpatient cost	1385 ± 3652 [498]	1766 ± 4243 [613]	0.3068
ER cost	181 ± 476 [0]	144 ± 515 [0]	0.4138
Prescription cost	937 ± 1236 [677]	926 ± 1065 [699]	0.9117
Total cost	5259 ± 14237 [1632]	4794 ± 10731 [1895]	0.6735
Total diabetes-related healthcare cost, mean ± SD [median]			
Inpatient cost	1304 ± 6588 [0]	811 ± 3447 [0]	0.2570
Outpatient cost	242 ± 321 [158]	274 ± 505 [131]	0.4393
ER cost	46 ± 216 [0]	34 ± 195 [0]	0.5346
Prescription cost	294 ± 293 [204]	285 ± 309 [154]	0.7474
Diabetes Supply cost	48 ± 97 [0]	46 ± 92 [0]	0.7766
Total cost	1934 ± 6551 [621]	1450 ± 3485 [596]	0.2658
Co-pay of Index Drug, n (%)			0.8694
	\$0–\$15	166 (46.6%)	87 (48.8%)
	\$15–\$30	147 (41.2%)	71 (39.8%)
	\$30+	42 (11.7%)	20 (11.2%)
Short-term disability, mean ± SD			
Occurrence count	0.12 ± 0.34	0.12 ± 0.37	0.9310
Days	3.10 ± 12.97	2.98 ± 12.9	0.9153
Cost	538 ± 2250	534 ± 2349	0.9856
Total cost (healthcare + short-term disability), mean ± SD	5797 ± 15005	5328 ± 12174	0.6987

Baseline information is collected within 3 months prior to index date. CDHP, consumer-driven health plan; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; ER, Emergency Room; HMO, health maintenance organization; NPH, neutral protamine Hagedorn insulin; OADs, oral antidiabetic drugs; POS point of service; PPO, preferred provider organization; SD, standard deviation.

### Persistence and adherence

During the 1-year follow-up, patients receiving insulin glargine were significantly more persistent (table 2) with and adherent to study medication compared with those in the NPH insulin cohort (table 2). Patients stayed on insulin glargine treatment for a significantly longer period (approximately 22 days longer) than those on NPH insulin. The Kaplan–Meier survival curve shows that patients treated with NPH insulin discontinued sooner than those treated with insulin glargine (log-rank test P-value=0.0073; figure 1). Sensitivity analyses using the 75th and 95th percentiles yielded similar results (75th percentile: 34.0% vs 28.1%, P=0.17; 95th percentile: 67.2% vs 57.9%, P=0.039). Both traditional and adjusted MPR values indicated a significantly better adherence to treatment with insulin glargine, compared with NPH insulin (table 2).

**Table 2. Follow-up treatment persistence, hypoglycemia, healthcare utilization and loss in productivity**

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Persistence/adherence, n (%) or mean ± SD			
Treatment persistence	186 (54.5)	75 (43.8)	0.0225

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Treatment persistence days	283.85 ± 96.92	261.77 ± 103.35	0.0178
MPR,	0.50 ± 0.28	0.45 ± 0.30	0.0418
Adjusted MPR	0.67 ± 0.33	0.61 ± 0.35	0.0380
DACON	30.6 ± 21.1	35.8 ± 31.9	0.0740
<b>Hypoglycemia, n (%) or mean ± SD</b>			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
<b>Healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	82 (23%)	56 (31.4%)	0.0360
Total hospitalization days	1.29 ± 4.54 [0]	2.06 ± 4.98 [0]	0.0754
# Hospitalizations/patient	0.28 ± 0.58 [0]	0.41 ± 0.73 [0]	0.0353
ER visits	104 (29.2%)	57 (32.0%)	0.5049
Endocrinologist visits	68 (19.1%)	48 (26.9%)	0.0377
Endocrinologist visits/patient	0.61 ± 1.57 [0]	0.94 ± 1.84 [0]	0.0422
Diabetes-related Hospitalizations	45 (12.6%)	27 (15.1%)	0.4201
Diabetes-related ER visits	43 (12.0%)	27 (15.1%)	0.3186
<b>Loss in productivity, mean ± SD</b>			
Short-term disability occurrences	0.36 ± 0.70	0.38 (0.70)	0.7944
Short-term disability days	15.96 ± 38.78	24.51 ± 60.33	0.0862

DACON, daily average consumption; ER, Emergency Room; NPH, neutral protamine Hagedorn insulin; SD, standard deviation

### Clinical outcomes

Clinical outcomes of the two agents were similar, both in terms of hypoglycemia-related event rates and DACON (table 2).

### Healthcare utilization and cost

During follow-up, patients in the insulin glargine cohort had lower rates of hospitalization and of endocrinologist visits, compared with those in the NPH insulin cohort (table 2). All diabetes-related healthcare utilization outcomes were similar between the cohorts (table 2). With respect to cost outcomes, the total overall healthcare costs were similar for the insulin glargine and NPH insulin cohorts, as were total diabetes-related healthcare costs. Similar total diabetes-related healthcare costs were reported despite significantly higher diabetes drug costs for the insulin glargine cohort, compared with the NPH insulin cohort (figure 2).

### Loss in productivity and its associated costs

The incidence of claims for short-term disability was similar between the insulin glargine and NPH insulin groups. However, the total number of short-term disability days and the associated cost were numerically lower in the insulin glargine group (16.0 vs 24.5 days,  $P=0.086$  and \$2,824 vs \$4,363,  $P=0.081$ , respectively; figure 2). Combined total costs were similar between the insulins (\$17,374 for insulin glargine vs \$20,455 for NPH insulin,  $P=0.204$ ).

### Correlations

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3 Significant correlations between a lower rate of treatment persistence and a higher likelihood  
4 of hospitalization (33.47% vs 22.22%,  $P=0.0045$ ) and short-term disability (60.1% vs 15.7%,  
5  $P < 0.001$ ) were found.  
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### 8 9 **Sensitivity analysis**

10 The sensitivity analyses using 1:1 ( $n=199$ , both cohorts) and 3:1 ( $n=480$ , insulin glargine;  
11  $n=160$ , NPH insulin) PSM yielded similar results overall (data not shown).  
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### 14 15 **DISCUSSION**

16 In this real-world study, use of insulin glargine was associated with better persistence and  
17 adherence than NPH insulin. In addition, lower healthcare resource utilization was  
18 associated with insulin glargine than NPH insulin, in terms of hospitalizations and  
19 endocrinologist visits, over 1 year of follow-up. Rates of hypoglycemia-related events were  
20 similar with the two treatments. Furthermore, diabetes drug-related costs were higher with  
21 insulin glargine than with NPH insulin, likely due to higher drug price of insulin glargine, and  
22 also the improved persistence/adherence associated with it. However, both total diabetes-  
23 related and total healthcare costs were similar in the two groups, as a consequence of the  
24 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated  
25 with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations  
26 and endocrinologist visits were also numerically lower in the group using insulin glargine but  
27 not statistically significant, probably due to sample size and the inaccuracy of using ICD-9-  
28 CM diagnosis code (250.xx) to capture diabetes-related events. In regard to short-term  
29 disability in both primary and sensitivity analyses, numerically fewer short-term disability  
30 days and lower associated costs were reported in the insulin glargine cohort than in the NPH  
31 insulin cohort, but this was not significant. It is likely that the reduction in short-term disability  
32 is related to better persistence with treatment in the insulin glargine cohort. Indeed, the  
33 correlation analysis showed that treatment persistence and short-term disability were highly  
34 correlated.  
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47 A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in  
48 patients with T2DM have indicated that insulin glargine represents an economic treatment  
49 option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at  
50 least as effective glycemic control as NPH insulin, and to be cost effective in a range of  
51 countries and settings.[33-39]  
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3 Basal insulin analogs have been shown to have several advantages compared to NPH  
4 insulin, including less pharmacologic variability, lower risk of hypoglycemia, and greater  
5 impact on quality of life.[18, 20, 21, 40] The rates of hypoglycemia-related events were,  
6 however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is  
7 associated with less hypoglycemia than NPH insulin,[20] the switch from NPH insulin to  
8 insulin glargine may usually be considered in patients with evidence of hypoglycemia or  
9 increasing incidence of hypoglycemic events. The baseline hypoglycemic event results  
10 between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort  
11 in the present analysis may be skewed to patients with lower NPH insulin-related  
12 hypoglycemia than expected.  
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20 The increased persistence associated with insulin glargine, as shown in this study, may lead  
21 to better clinical outcomes,[41] and potentially improve work-related outcomes.[9, 12, 19]  
22 Diabetes-related disability has been shown to result in loss of work-place productivity.[42-46]  
23 In this study, we observed fewer short-term disability days in patients on insulin glargine,  
24 compared with those on NPH insulin. Although the differences were not statistically  
25 significant, this finding may suggest that initiation of therapy with insulin glargine could help  
26 increase workplace productivity among employed patients with T2DM compared with those  
27 initiating with NPH insulin.  
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33 As with all retrospective studies, issues of sampling bias should be taken into account when  
34 interpreting these results, which may introduce selection bias. The use of PSM methodology  
35 in this study should have helped reduce the impact of selection bias. In fact, three different  
36 matching ratios were tested, and all yielded similar findings. However, PSM likely limited  
37 patients in the insulin glargine cohort to those most similar to the NPH insulin cohort and not  
38 to those patients with T2DM who use insulin in general. Further, some insulin patients may  
39 have been missed due to the availability of 90-day/mail order prescriptions resulting in their  
40 being missed during the 3-month baseline period.  
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47 This study has several limitations. Although the MarketScan data represent a large diverse  
48 population, the study only included information from mainly large, self-insured employers,  
49 whose employees were more likely to be located in certain geographic areas than the  
50 general employee population, and the analysis included a convenience sample of patients  
51 whose employer supplied productivity data. Therefore, this study should not be assumed to  
52 be representative of the overall US population. As with any retrospective observational  
53 study, causality of treatment effects cannot be established in this study. Although the PSM  
54 method was used to balance differences between the two groups included in the study,  
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3 confounding by indication or prognosis may still have affected the outcomes observed. The  
4 use of PSM also led to a significant reduction in the sample size, particularly in the insulin  
5 glargine group, due to the required matching ratios, and a much smaller sample size in the  
6 NPH group. This may also make the study underpowered to detect all significant differences  
7 between treatment groups. In addition, the similar rate of hypoglycemia observed between  
8 groups is inconsistent with existing literature, as previous studies suggest a lower risk of  
9 hypoglycemia with insulin glargine, compared with NPH insulin.[15, 33] It is unlikely that  
10 rates of hypoglycemia would be captured with the same level of sensitivity in this  
11 retrospective analysis as they would in a randomized clinical trial. Moreover, the low overall  
12 hypoglycemia rate in both cohorts may have resulted in insufficient statistical power to detect  
13 significant differences. Coding issues in the claim data may also have contributed to the lack  
14 of statistical robustness. The DACON was measured based on pharmacy claim data and  
15 may not be accurate. For example, patients on a low dose are instructed to discard unused  
16 insulin (particularly in vials) after approximately 1 month; hence, pharmacy claim data can  
17 lead to an overestimation of DACON. However, this is unlikely to affect the study groups  
18 disproportionately because they were similar in proportion of patients using insulin pens (table  
19 2). A1C data were not available, so neither the effectiveness of glycemetic control nor the  
20 association with hypoglycemia could be assessed. Finally, the 12-month follow-up period of  
21 this study may not have been sufficient to detect benefits due to improved persistence and  
22 adherence.  
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### 35 **CONCLUSION**

36 This study showed that insulin glargine resulted in better persistence and adherence, with  
37 lower health care utilization, at similar total healthcare costs despite higher drug-related  
38 costs, than NPH insulin. Better persistence and adherence may lead to long-term health  
39 benefits and additional benefits to patients with T2DM and their employers. Due to the  
40 retrospective nature of this study, further studies need to be conducted to confirm these  
41 findings.  
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### 47 **ACKNOWLEDGEMENTS**

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### 52 **DISCLOSURES**

53 LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis  
54 U.S.  
55  
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57 RM and WW: Employees of sanofi-aventis U.S.  
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**CONTRIBUTIONS**

LW: Active in study design, statistical plan, data analysis, drafting, and review of manuscript.

WW: Active in creating the concept and study design, drafting, and review of manuscript.

RM: Active in creating the concept and study design, drafting, and review of manuscript.

LX: Role in statistical analysis and review of manuscript.

OB: Active in creating the study design, statistical plan, and review of manuscript.

**DATA SHARING**

Additional data are available by e-mailing Dr Onur Baser [obaser@statinmed.com](mailto:obaser@statinmed.com)



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3 **Figure 1** Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin  
4 glargine and NPH insulin  
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8 **Figure 2** 1-year short-term disability and direct healthcare costs. (Total between-group  
9 differences did not reach statistical significance).  
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11 \*P<0.0001 vs insulin glargine  
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**Additional File 1**

EVEREST Statement: Checklist for health economics paper

	<b>Study Section</b>	<b>Additional Remarks</b>
<b>Study Design</b>		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction/Methods/discussion	
(6) The form of economic evaluation used is stated	Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction/Methods/discussion	
<b>Data Collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Methods/results	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	Methods/Results	
(14) Productivity changes (if included) are reported	Results/Methods	Effect on productivity

	Study Section	Additional Remarks
separately		is estimated by the length/cost of claims for short term disability
(15) The relevance of productivity changes to the study question is discussed	Introduction/discussion	
(16) Quantities of resources are reported separately from their unit costs	N/A	
(17) Methods for the estimation of quantities and unit costs are described	N/A	
(18) Currency and price data are recorded	Results	
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
<b>Analysis and Interpretation of Results</b>		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods/Results	
(28) The choice of variables for sensitivity analysis is justified	N/A	
(29) The ranges over which the variables are varied are stated	Results	
(30) Relevant alternatives are compared	Results	



	<b>Study Section</b>	<b>Additional Remarks</b>
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results/discussion	
(34) Conclusions follow from the data reported	Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion	

**Title:**

Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study

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## Article Summary

### Article Focus

- Do differences seen in the outcomes of randomized controlled trials comparing insulin glargine and neutral protamine Hagedorn (NPH) translate to improved real-world outcomes in employed adults living in the United States?

### Key Messages

- Insulin glargine was associated with better persistence, lower inpatient admission, which offsets its higher drug cost, and lower indirect costs from short-term disability, than NPH insulin.
- Reduced short-term disability and improved adherence with insulin glargine may improve long-term productivity, compared with NPH insulin, and provide benefits to both employees and their employers.

### Strengths and Limitations

- *Strengths*
  - The MarketScan database represents a large and diverse data source.
  - The database captures detailed information on both employees' healthcare resource utilization and their productivity, as measured by short-term disability.
  - The use of propensity-score-matching methodology reduces treatment selection bias between insulin glargine and NPH groups.
  - ~~The use of propensity-score-matching methodology reduces confounding by indication as and treatment selection bias between insulin glargine and NPH groups.~~
  - Sensitivity analysis confirmed the consistency of findings.
- *Limitations:*
  - As with all retrospective studies, causality of treatment effects cannot be established in this study. This study used a convenience sample, so it is not representative of the overall US population, and also may be underpowered to detect all significant differences between groups.
  - Confounding by indication or prognosis may be a source of bias in this retrospective observational study.
  - ~~—~~
  - It is unlikely that rates of hypoglycemia and other clinical outcomes would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, A1C data were not available,

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For peer review only

**[Abstract]****Limit: 300 words****Current: ~~299~~ 2989 words**

**Objectives:** To compare real-world outcomes of initiating insulin glargine (GLA) versus neutral protamine Hagedorn (NPH) insulin among employees with type 2 diabetes mellitus (T2DM) who had both employer-sponsored health insurance and short-term-disability coverages.

**Design:** Retrospective cohort study

**Setting:** MarketScan Commercial Claims and Encounters/Health and Productivity Management Databases 2003–2009.

**Participants:** Adult employees with T2DM who were previously treated with oral antidiabetic drugs and/or glucagon-like-peptide 1 receptor agonists, and initiated GLA or NPH were included if they were continuously enrolled in healthcare and short-term-disability coverages for 3 months before (baseline) and 1-year after (follow-up) initiation. ~~Confounding by indication~~ ~~Treatment s~~ ~~Selection bias~~ was addressed by 2:1 propensity score matching (PSM). Sensitivity analyses were conducted using different matching ratios.

**Primary and secondary outcome measures:** Outcomes during 1-year follow-up were measured and compared: insulin treatment persistence and adherence; hypoglycemia rates and daily average consumption of insulin; total and diabetes-specific healthcare resource utilization and costs; and loss in productivity, as measured by short-term disability, and the associated costs.

**Results:** A total of 534 patients were matched and analyzed (GLA: 356; NPH 178) with no significant differences in baseline characteristics. GLA patients were more persistent and adherent (both  $P < 0.05$ ), had lower rates of hospitalization (23.0% vs 31.4%;  $P = 0.036$ ) and

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7 endocrinologist visits (19.1% vs 26.9%;  $P=0.038$ ), similar hypoglycemia rates (both 4.4%;  
8  $P=1.0$ ), higher diabetes drug costs (\$2,031 vs \$1,522;  $P<0.001$ ), but similar total healthcare  
9 costs (\$14,550 vs \$16,093;  $P=0.448$ ) and total diabetes-related healthcare costs (\$4,686 vs  
10 \$5,604;  $P=0.416$ ). Short-term disability days and costs were numerically lower in the GLA  
11 cohort (16.0 vs 24.5 days;  $P=0.086$  and \$2,824 vs \$4,363;  $P=0.081$ , respectively). Sensitivity  
12 analysis yielded similar findings.  
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16 **Conclusion:**

17 Insulin glargine results in better persistence and adherence, compared with NPH insulin,  
18 with no overall cost disadvantages. Better persistence and adherence may lead to long-term  
19 health benefits for employees with T2DM.  
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## INTRODUCTION

In the United States (US), diabetes affects an estimated 25.8 million people (8.3% of the US population).[1] Type 2 diabetes mellitus (T2DM) and associated comorbidities are associated with disability, reduced productivity, and work loss,[2, 3] which impose an important economic burden on self-insured employers.[4] The diabetes-related economic burden from lost productivity and disability for employees and employers is substantial. Overall, reduced national productivity related to diabetes accounted for \$58 billion in 2007 in the US,[5] while in a more recent study diabetes accounted for 1,473,000 disability-adjusted life years.[6]

~~Early improvements in glucose control can reduce the long-term risk of complications associated with T2DM.[7] Adherence to anti-hyperglycemic medication interventions is also associated with improved glycemic control and decreased healthcare resource utilization[448] and, consequently, may improve outcomes. Adherence to medication~~ also reduces the incidence of complications, and is thus associated with improved work-related outcomes, such as reducing the number of short-term disability days.[209] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[2410, 2211] People with untreated diabetes, or those with a long duration of the disease, are at increased risk of occupational injury, which is minimized in treated patients who are adherent to medication.[2312] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[2410, 2413]

A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides clinically relevant improvements in glycemic control with a good safety profile.[714] ~~In addition, early improvements in glucose control can reduce the long-term risk of complications.[8]~~ Options for basal insulin include insulin glargine, a long-acting basal insulin analog, or ~~Neutral-neutral Protamine-protamine~~ Hagedorn (NPH) insulin, an intermediate-acting insulin. Clinical studies have shown that the efficacy of these two agents is similar, but that there is a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, with insulin glargine.[915-1117]

Simplicity and convenience of treatment regimens are important for those initiating insulin therapy. Insulin glargine was approved for once-daily injection and may have implications for increased patient persistence and adherence.[1218] ~~Although~~ However, twice-daily use of insulin glargine might be required to achieve therapeutic goals in some patients with T2DM.[1319] ~~Adherence is also associated with improved glycemic control and decreased healthcare resource utilization[14] and, consequently, may improve outcomes.~~ Other insulin

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7 therapy options, such as insulin detemir and insulin lispro protamine suspension, also have  
8 convenience and outcomes benefits which may contribute to improved persistence and  
9 adherence.<sup>[4520-4722]</sup> In reality, patients taking insulin glargine have been shown to be  
10 more likely to persist with their medication than those taking NPH insulin.<sup>[4823]</sup> In general,  
11 treatment complexity for chronic conditions – including, though not limited to the need to  
12 administer more than one injection daily – correlates with poor adherence.<sup>[4924]</sup>  
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17 Although there are data in support of the clinical benefits of basal insulins, there is currently  
18 a paucity of real-world information about the impact of different basal insulin regimens on  
19 healthcare utilization, employee disability, and their associated costs from an employer's  
20 perspective. This analysis was performed in order to provide-compare real-world outcomes  
21 from initiating insulin glargine or NPH insulin among employees with T2DM who had both  
22 employer-sponsored health insurance and short-tem-disability coverages. As insulin detemir,  
23 another long-acting basal insulin analog, was only launched in the US in 2006, too few  
24 patients were being treated with this agent for it to be included in the analysis as a  
25 comparator.  
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## 32 METHODS

### 33 Database

34 This study is a retrospective analysis from the employer perspective, of patients' medical  
35 and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters  
36 Database 2003–2009. This database captures person-specific clinical utilization,  
37 expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out  
38 services from about 100 large employers, health plans, and government and public  
39 organizations.  
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43 Short-term disability data were extracted from the MarketScan Health and Productivity  
44 Management Database, which is an integrated database that contains information on  
45 absence, short-term disability, and workers' compensation experience. This information is  
46 linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial  
47 Claims and Encounters Database for these employees, providing a unique and valuable  
48 resource for examining health and productivity issues for an employed, privately insured  
49 population.  
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7 The MarketScan Research Databases are fully compliant with the letter and spirit of the  
8 Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board  
9 review was waived.  
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### 11 **Cohort selection criteria**

12 Included in the analysis were employees, but not their dependents, of 18 years of age or  
13 older with T2DM, defined as having made at least one inpatient visit or two physician visits  
14 dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type  
15 II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th  
16 Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or  
17 unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine  
18 or NPH insulin with the date of the first such claim being the index date (prescriptions of  
19 other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare  
20 benefits and work benefits for short-term disability for 3 months prior to insulin initiation  
21 (baseline period); and 12 months after insulin initiation (follow-up period); and on at least one  
22 oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The  
23 patient cohorts for comparison were determined on the basis of use of insulin glargine or  
24 NPH insulin at initiation of insulin therapy. Patients initiating insulin detemir were excluded  
25 from the current study because it was only available after 2005<sup>76</sup>, and thus an insufficient  
26 number of patients (fewer than 100) was identified in the database to provide adequate  
27 statistical power for meaningful comparisons. Outcomes were compared between the  
28 matched cohorts after 1 year of follow-up.  
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### 37 **Baseline characteristics**

38 Data were analyzed to assess baseline characteristics, including: gender; age; OAD use;  
39 comorbidities; healthcare utilization/costs; index drug co-pay, and short-term disability for  
40 3 months prior to insulin initiation for all patients. Follow-up records were analyzed to assess  
41 treatment persistence, adherence, hypoglycemic events, healthcare resource utilization,  
42 cost, and short-term disability after initiation of insulin therapy.  
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### 46 **Persistence and Adherence**

47 Measuring persistence with insulin treatment is challenging due to its non-fixed dose  
48 schedule. Consistent with previously published studies,<sup>[25-27]</sup> persistence was measured  
49 here as the time the patient had remained on study drugs without discontinuation or  
50 switching following insulin initiation. Study medication was considered discontinued if the  
51 prescription was not refilled within the expected time of medication coverage, defined as the  
52 90th percentile of the time, stratified by the metric quantity supplied, between the first and  
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7 second fills among patients with at least one refill. For example, our analysis showed that for  
8 patients who filled a prescription for 10 mL and refilled later, 90% of ~~GLA-insulin glargine~~  
9 patients refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient  
10 was considered ~~discontinuing to have discontinued GLA-insulin glargine~~ if he/she previously  
11 filled a prescription for 10mL of ~~GLA-insulin glargine~~ but did not refill it within 119 days.  
12 Patients who restarted their initial medication after discontinuation, as defined above, were  
13 also considered non-persistent patients. Sensitivity analyses were also conducted using the  
14 75th and 95th percentiles of the time.  
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18 Treatment adherence was measured during the 1-year follow-up by both the traditional  
19 medication possession ratio (MPR) and the adjusted MPR, which allows for differences in  
20 insulin-device package size [28] (insulin glargine, for example, is packaged either in 10 mL  
21 vials with a total of 1,000 units, or in a 3 mL disposable device in a package of 5 pens with a  
22 total of 1,500 units) to correct the issue that almost all prescriptions are dispensed with a 30-  
23 day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying  
24 the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in  
25 the analysis period divided by the number of days in the analysis period) by the average  
26 number of days between insulin study drug prescription refills for patients using the insulin  
27 divided by the average days' supply for patients using the insulin. By using data based on  
28 the actual gap between the days' supply and the days to next refill, this adjustment is  
29 necessary to measure real adherence to doctor's instructions.  
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### 36 **Clinical outcomes**

37 Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency  
38 department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia  
39 (ICD-9 code 250.8—diabetes with other specified manifestations; 251.0—hypoglycemic coma;  
40 251.1—other specified hypoglycemia; or 251.2—hypoglycemia, unspecified).[29] Daily  
41 average consumption (DACON) of insulin was estimated based on pharmacy claims data  
42 and calculated as the total number of units dispensed before the last refill of study drug  
43 divided by the total number of days between initiation and last refill during follow-up period.  
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46 ~~Glycated hemoglobin (A1C)~~ data were not available in this study.  
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### 49 **Healthcare resource utilization and cost**

50 Categories of healthcare resource utilization included numbers of outpatient visits,  
51 emergency room (ER) visits, ~~and~~ inpatient admissions, inpatient length of stay (days), ~~and~~  
52 total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare  
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resource utilization included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx), and use of anti-hyperglycemic medications, glucose meters, and supplies.

Healthcare costs were computed as paid amounts of adjudicated claims, including insurer and health-plan payments, copayments, and deductibles. Diabetes-specific healthcare costs included those related to a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx).

### Loss in productivity and its associated costs

Loss in productivity was measured by the total number of days patients were on short-term disability during the baseline and follow-up periods. The associated costs for short-term disability were calculated as 70% of \$240 (a figure reflecting the average daily wage paid to employees of large employers),<sup>[30]</sup> which amounts to \$168, since disability programs typically pay for 70% of lost income.<sup>[31]</sup>

### Total cost

Total cost was assessed by combining direct costs (healthcare costs) and indirect costs (short-term disability costs), and comparisons between groups were made. Costs were adjusted for inflation to 2010 US dollars using the medical care component of the Consumer Price Index.

### Statistical analyses

To reduce the observed baseline selection bias, such as confounding by indication, between the two study cohorts, propensity score matching (PSM) methodology [32] was implemented, with a stringent 2:1 matching of patients initiating insulin glargine or NPH insulin. Propensity scores for initiating insulin glargine vs-versus NPH were calculated from a logistic regression model that estimated the likelihood of initiating insulin glargine based on the observed patient characteristics. Covariates were selected based on their hypothesized confounding relationship with the outcome variables, and included age, gender, region, health plan type, Charlson Comorbidity Index, and baseline concomitant medications, hypoglycemic events, healthcare utilization (overall or disease-related), co-pays, and healthcare cost (overall or disease-related). Sensitivity analyses were also conducted using 1:1 and 3:1 PSM.

Among the matched cohorts, all study variables, including baseline and outcome measures, were analyzed descriptively. Results were stratified by treatment cohort. For dichotomous variables, P values were calculated according to the Mann–Whitney U test; for continuous variables, t tests were used to calculate P values. P values of <0.05 were taken to be

~~indicative of a significant difference.~~ Kaplan–Meier survival curves and the log-rank test were used to compare 1-year treatment persistence. ~~The relationship~~ Relationships between ~~treatment persistence and~~ hospitalization ~~and as well as~~ short-term disability ~~was were~~ investigated by the chi-squared test ~~and Pearson's correlation analysis.~~ P values of <0.05 were taken to be indicative of a significant difference.

## RESULTS

### Baseline characteristics

Data from 2,454 patient records were eligible for the 1-year follow-up analyses: 2,250 in the insulin glargine (~~GLA~~) cohort, and 204 in the NPH insulin (~~NPH~~) cohort. Before the matching, ~~GLA~~-patients using insulin glargine were more likely to be male, older, using insulin pen, and ~~had have~~ higher copayment than ~~NPH those using NPH patients~~ (data not shown here), ~~indicating confounding by indication as selection bias.~~ The 2:1 PSM yielded a total of 534 patients (~~GLA~~insulin glargine, ~~n~~=356; NPH ~~insulin~~, ~~n~~=178) with well-matched baseline characteristics (table 1). ~~Overall, 43.8% of the patients included in the analysis were women; mean age was 49 years (range: 20–64 years), and the mean number of OADs was 1.8. The baseline hospitalization rate was 15.2%, with a mean short term disability of 3.0 days.~~

**Table 1.** Baseline characteristics (3 months prior to index)

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Gender, female (%)	153 (42.9%)	81 (45.5%)	0.5789
Age, years, mean ± SD	49 ± 10	49 ± 10	0.7580
	18–39, n (%) 77 (21.6%)	35 (19.6%)	0.5988
	40–64, n (%) 279 (78.3%)	143 (80.3%)	0.5988
Health plan, n (%)			0.9390
	CDHP 5 (1.4%)	2 (1.1%)	
	Comprehensive 34 (9.5%)	18 (10.1%)	
	HMO 63 (17.6%)	36 (20.2%)	
	POS 65 (18.2%)	29 (16.2%)	
	PPO 189 (53.0%)	93 (52.2%)	
Region, n (%)			
	North Central Region 82 (23.0%)	45 (25.2%)	0.5653
	Northeast Region 58 (16.2%)	32 (17.9%)	0.6238
	South Region 129 (36.2%)	54 (30.3%)	0.1758
	West Region 85 (23.8%)	45 (25.2%)	0.7215
	Unknown 2 (0.5%)	2 (1.1%)	0.4778
<del>Insulin</del> Pen use <u>for Initiated Insulin</u> , n (%)	59 (16.5%)	33 (18.5%)	0.8694
Antidiabetic drugs, n (%)			
	Metformin 262 (73.5%)	132 (74.1%)	0.8893
	Sulfonylureas 223 (62.6%)	105 (58.9%)	0.4138
	Thiazolidinediones 133 (37.3%)	68 (38.2%)	0.8497
	DPP-4 inhibitors 9 (2.5%)	6 (3.3%)	0.5785
	Exenatide 30 (8.4%)	11 (6.1%)	0.3579
Number of OADs, mean ± SD	1.81 ± 0.73	1.80 ± 0.75	0.9015
Charlson Comorbidity Index, mean ± SD	0.284 ± 0.819	0.281 ± 1.159	0.9770
Comorbidities, n (%)			

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	Insulin glargine (n=356)	NPH insulin (n=178)	P value
<b>Obesity</b>	<b>5 (1.4)</b>	<b>4 (2.2)</b>	<b>0.4758</b>
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
<b>Congestive heart failure</b>	<b>12 (3.3)</b>	<b>4 (2.2)</b>	<b>0.4728</b>
Retinopathy	7 (1.9)	5 (2.8)	0.5357
Neuropathy	19 (5.3)	8 (4.4)	0.6752
Nephropathy	15 (4.2)	3 (1.6)	0.1270
<b>Total_H</b> healthcare utilization, n (%) or mean $\pm$ SD [median]			
<b>All-cause</b> Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
<b>All-cause</b> Total hospitalization days	0.97 $\pm$ 3.38 [0]	0.72 $\pm$ 2.11 [0]	0.3018
<b>All-cause</b> ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	25 (14.0%)	0.2550
Hospitalization/patient	0.16 $\pm$ 0.39 [0]	0.17 $\pm$ 0.42 [0]	0.6468
ER visits/patient	0.31 $\pm$ 0.67 [0]	0.28 $\pm$ 0.68 [0]	0.6817
Endocrinologist visits/patient	0.15 $\pm$ 0.48 [0]	0.19 $\pm$ 0.55 [0]	0.3844
<b>Diabetes-related</b> healthcare utilization, n (%) or mean $\pm$ SD [median]			
<b>Diabetes-related</b> Hospitalizations	34 (9.5%)	20 (11.2%)	0.5426
<b>Diabetes-related</b> Total hospitalization days	0.52 $\pm$ 2.31 [0]	0.41 $\pm$ 1.49 [0]	0.4975
<b>Diabetes-related</b> ER visits	37 (10.3%)	17 (9.5%)	0.7608
Endocrinologist visits	36 (10.1%)	23 (12.9%)	0.3290
Office visits	297 (83.4%)	138 (77.5%)	0.0982
Hospitalizations/patient	0.10 $\pm$ 0.29	0.11 $\pm$ 0.32	0.5434
ER visits/patient	0.13 $\pm$ 0.40 [0]	0.11 $\pm$ 0.34 [0]	0.5670
Endocrinologist visits/patient	0.14 $\pm$ 0.47 [0]	0.17 $\pm$ 0.53 [0]	0.4951
Office visits/patient	1.74 $\pm$ 1.43 [1]	1.60 $\pm$ 1.44 [1]	0.2782
Total hospitalization days	0.52 $\pm$ 2.31 [0]	0.41 $\pm$ 1.49 [0]	0.4975
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean $\pm$ SD [median]			
Inpatient cost	2756 $\pm$ 12393 [0]	1958 $\pm$ 8241 [0]	0.3766
Outpatient cost	1385 $\pm$ 3652 [498]	1766 $\pm$ 4243 [613]	0.3068
ER cost	181 $\pm$ 476 [0]	144 $\pm$ 515 [0]	0.4138
Prescription cost	937 $\pm$ 1236 [677]	926 $\pm$ 1065 [699]	0.9117
Total cost	5259 $\pm$ 14237 [1632]	4794 $\pm$ 10731 [1895]	0.6735
Total diabetes-related healthcare cost, mean $\pm$ SD [median]			
Inpatient cost	1304 $\pm$ 6588 [0]	811 $\pm$ 3447 [0]	0.2570
Outpatient cost	242 $\pm$ 321 [158]	274 $\pm$ 505 [131]	0.4393
ER cost	46 $\pm$ 216 [0]	34 $\pm$ 195 [0]	0.5346
Prescription cost	294 $\pm$ 293 [204]	285 $\pm$ 309 [154]	0.7474
Supply cost	48 $\pm$ 97 [0]	46 $\pm$ 92 [0]	0.7766
Total cost	1934 $\pm$ 6551 [621]	1450 $\pm$ 3485 [596]	0.2658
Co-pay of Index Drug, n (%)			0.8694
\$0-\$15	166 (46.6%)	87 (48.8%)	
\$15-\$30	147 (41.2%)	71 (39.8%)	
\$30+	42 (11.7%)	20 (11.2%)	
Unknown	1 (0.2%)	0 (0.0%)	
Short-term disability, mean $\pm$ SD			
Occurrence count	0.12 $\pm$ 0.34	0.12 $\pm$ 0.37	0.9310
Days	3.10 $\pm$ 12.97	2.98 $\pm$ 12.9	0.9153
Cost	538 $\pm$ 2250	534 $\pm$ 2349	0.9856
Total cost (healthcare + short-term disability), mean $\pm$ SD	5797 $\pm$ 15005	5328 $\pm$ 12174	0.6987

Baseline information is collected within 3 months prior to index date. CDHP, consumer-driven health plan; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase-4; ER, Emergency Room; HMO, health maintenance organization; NPH, neutral protamine Hagedorn insulin; OADs, oral antidiabetic drugs; POS point of service; PPO, preferred provider organization; SD, standard deviation.

**Persistence and adherence**

During the 1-year follow-up, patients receiving insulin glargine were significantly more persistent (table 2, [figure 4](#)) with and adherent to study medication compared with those in the NPH insulin cohort (table 2). ~~Over half (54.5%) of patients on insulin glargine were persistent, compared with 43.8% of those on NPH (P=0.0225).~~ Patients stayed on insulin glargine treatment for a significantly longer period (approximately 22 days longer) than those on NPH insulin (~~284 vs 262 days, P=0.0178~~). The Kaplan–Meier survival curve shows that patients treated with NPH insulin discontinued sooner than those treated with insulin glargine (log-rank test P-value=0.0073; figure [21](#)). Sensitivity analyses using the 75th and 95th percentiles yielded similar results, ~~with all indicating better persistence with insulin glargine compared with NPH insulin~~ (75th percentile: 34.0% vs 28.1%, P=0.17; 95th percentile: 67.2% vs 57.9%, P=0.039). Both traditional and adjusted MPR values indicated a significantly better adherence to treatment with insulin glargine, compared with NPH insulin (table 2, [figure 4](#)).

**Table 2. Follow-up treatment persistence, hypoglycemia, healthcare utilization and loss in productivity**

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
<b>Persistence/adherence, n (%) or mean ± SD</b>			
Treatment persistence	186 (54.5)	75 (43.8)	0.0225
Treatment persistence days	283.85 ± 96.92	261.77 ± 103.35	0.0178
MPR	0.50 ± 0.28	0.45 ± 0.30	0.0418
Adjusted MPR	0.67 ± 0.33	0.61 ± 0.35	0.0380
DACON	30.6 ± 21.1	35.8 ± 31.9	0.0740
<b>Hypoglycemia, n (%) or mean ± SD</b>			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
<b>Total <u>H</u>healthcare utilization, n (%) or mean ± SD</b>			
Hospitalizations	82 (23%)	56 (31.4%)	0.0360
<u>Total hospitalization days</u>	<u>1.29 ± 4.54 [0]</u>	<u>2.06 ± 4.98 [0]</u>	<u>0.0754</u>
<u># Hospitalizations/patient</u>	<u>0.28 ± 0.58 [0]</u>	<u>0.41 ± 0.73 [0]</u>	<u>0.0353</u>
ER visits	104 (29.2%)	57 (32.0%)	0.5049
Endocrinologist visits	68 (19.1%)	48 (26.9%)	0.0377
Office visits	352 (98.8%)	177 (99.4%)	0.5251
Hospitalizations/patient	0.28 ± 0.58 [0]	0.41 ± 0.73 [0]	0.0353
ER visits/patient	0.56 ± 1.43 [0]	0.54 ± 1.03 [0]	0.8353
Endocrinologist visits/patient	0.61 ± 1.57 [0]	0.94 ± 1.84 [0]	0.0422
Office visits/patient	18.37 ± 17.43 [14]	18.30 ± 14.98 [14]	0.9615
Total hospitalization days	1.29 ± 4.54 [0]	2.06 ± 4.98 [0]	0.0754
<b>Diabetes-related healthcare utilization, n (%) or mean ± SD</b>			
<u>Diabetes-related Hospitalizations</u>	45 (12.6%)	27 (15.1%)	0.4201
<u>Diabetes-related ER visits</u>	43 (12.0%)	27 (15.1%)	0.3186
Endocrinologist visits	68 (19.1%)	45 (25.2%)	0.0993
Office visits	341 (95.7%)	168 (94.3%)	0.4689
Hospitalizations/patient	0.14 ± 0.38 [0]	0.15 ± 0.36 [0]	0.6804
ER visits/patient	0.20 ± 0.81 [0]	0.16 ± 0.40 [0]	0.5207
Endocrinologist visits/patient	0.56 ± 1.45 [0]	0.80 ± 1.65 [0]	0.1100
Office visits/patient	5.69 ± 3.98 [5]	5.56 ± 4.23 [5]	0.7293
Total hospitalization days	0.56 ± 2.50 [0]	0.53 ± 1.09 [0]	0.8650
<b>Loss in productivity, mean ± SD</b>			

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	Insulin glargine (n=356)	NPH insulin (n=178)	P value
Short-term disability occurrences	0.36 ± 0.70	0.38 (0.70)	0.7944
Short-term disability days	15.96 ± 38.78	24.51 ± 60.33	0.0862

DACON, daily average consumption; ER, Emergency Room; NPH, neutral protamine Hagedorn insulin; SD, standard deviation

### Clinical outcomes

Clinical outcomes of the two agents were similar, both in terms of hypoglycemia-related event rates (~~both cohorts had overall hypoglycemia rates of 4.4%; P=1.0~~) and DACON (~~insulin glargine: 30.6 units vs NPH insulin: 35.8 units, P=0.074~~) (table 2).

### Healthcare utilization and cost

~~In terms of total healthcare utilization and cost, During follow-up, patients in the insulin glargine cohort also had lower rates of hospitalization and of endocrinologist visits, compared with those in the NPH insulin cohort (23.0% vs 31.4%; P=0.036, respectively; table 2), and of endocrinologist visits (19.1% vs 26.0%; P=0.038 table 2), despite similar utilization at baseline (table 1).~~ All diabetes-related healthcare utilization outcomes were similar between the cohorts (table 2). With respect to cost outcomes, the total overall healthcare costs were similar for the insulin glargine and NPH insulin cohorts (~~\$14,550 vs \$16,093, respectively; P=0.448~~), as were total diabetes-related healthcare costs (~~\$4,686 vs \$5,604; P=0.416~~) (figure 3). Similar total diabetes-related healthcare costs were reported despite significantly higher ~~diabetes drug diabetes-related prescription~~ costs for the insulin glargine cohort (~~-\$2,031~~), compared with the NPH insulin cohort ~~(figure 23) (\$1,522) (P<0.001)~~.

### Loss in productivity and its associated costs

~~In terms of loss in productivity and the associated costs for employers, The~~ incidence of claims for short-term disability was ~~similar between 0.36 per patient per year in the insulin glargine group, compared with 0.38 and in the NPH insulin groups (P=0.7944)~~. However, the total number of short-term disability days and the associated cost were numerically lower in the insulin glargine group (16.0 vs 24.5 days; ~~P=0.086 and \$2,824 vs \$4,363; P=0.081, respectively; figure 32~~). Combined total costs were similar between the insulins (\$17,374 for ~~GLA-insulin glargine~~ vs \$20,455 for NPH ~~insulin~~; ~~P=0.204~~).

### Correlations

~~Significant correlations between a lower rate of treatment persistence and a higher likelihood of hospitalization (33.47% vs 22.22%, P=0.0045) and short-term disability (60.1% vs 15.7%, P <0.001) were found (The chi squared tests showed ) significant correlations~~



between lower rate of treatment persistence and higher likelihood of hospitalization (33.47% vs. 22.22%, P=0.0045) and short term disability (60.1% vs. 15.7%, P<0.001).

In the 2:1 matched cohorts, the chi-squared tests showed that patients who were not persistent with their insulin treatment were significantly more likely to have a claim for short-term disability (33.47% vs. 22.22%, P=0.0045), and so were those with hospitalizations (60.1% vs. 15.7%, P<0.001). Pearson's correlation test showed that higher number of insulin persistence days was correlated with lower number of short term disability days ( $r=-0.1325$ , P=0.0027), while higher number of hospitalizations was correlated with higher number of short term disability claims ( $r=0.40$ , P<0.0001).

### Sensitivity analysis

The sensitivity analyses using 1:1 (n=199, both cohorts) and 3:1 (n=480, insulin glargine: n=160, NPH insulin) PSM yielded similar results overall (data not shown). In the 1:1 PSM analysis (n=199, both cohorts), persistence with treatment was higher with insulin glargine than with NPH insulin (75th percentile: 32.8% vs 26.0%, P=0.146; 90th percentile: 51.0% vs 41.1%, P=0.052; 95th percentile: 66.1% vs 54.6%, P=0.022). Treatment adherence was also higher with insulin glargine than with NPH insulin (MPR: 0.49 vs 0.43, P=0.039; adjusted MPR: 0.66 vs 0.60; P=0.070). A significantly lower hospitalization rate (26.1% vs 36.1%, P=0.030), lower endocrinologist visit rate (17.0% vs 26.1%, P=0.028), fewer hospitalization days (1.32 vs 2.29 days, P=0.026), fewer short term disability days and lower associated costs (12.33 days vs 27.67 days; P=0.002 and \$2,173 vs \$4,942; P=0.002, respectively) were reported with insulin glargine than with NPH insulin in the 1:1 PSM analysis. Total costs in the 1:1 matched cohort were also significantly lower in the GLA cohort than in the NPH cohort (\$15,720 vs \$21,398, P=0.022). The results from the 3:1 PSM analysis (n=480, insulin glargine; n=160, NPH insulin) were consistent with those from the 2:1 PSM analysis.

### DISCUSSION

In this real-world study, use of insulin glargine was associated with better persistence and adherence than NPH insulin. In addition, a lower healthcare resource utilization was associated with insulin glargine than NPH insulin, in terms of hospitalizations and endocrinologist visits, over 1 year of follow-up. Rates of hypoglycemia-related events were similar with the two treatments. Furthermore, diabetes drug-related costs were higher with insulin glargine than with NPH insulin, likely due to higher drug price of insulin glargine, and also the improved persistence/adherence associated with it. However, both total diabetes-related and total healthcare costs were similar in the two groups, as a consequence of the



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7 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated  
8 with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations  
9 and endocrinologist visits were also numerically lower in ~~GLA the~~ group using insulin  
10 glargine but not statistically significant, probably due to sample size and the inaccuracy of  
11 using ICD-9-CM diagnosis code (250.xx) to capture diabetes-related events. In regard to  
12 short-term disability in both primary and sensitivity analyses, numerically fewer short-term  
13 disability days and lower associated costs were reported in the insulin glargine cohort than in  
14 the NPH insulin cohort, but this was not significant. It is likely that the reduction in short-term  
15 disability is related to ~~fewer hospitalizations~~ better persistence with treatment in the insulin  
16 glargine cohort. Indeed, the correlation analysis showed that treatment persistence and  
17 short-term disability were highly correlated, ~~that patients with any hospitalizations were~~  
18 ~~significantly more likely to claim for short term disability: both the number and duration of~~  
19 ~~hospitalizations were highly correlated with the number of claims and the duration of short-~~  
20 ~~term disability.~~

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26 A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in  
27 patients with T2DM have indicated that insulin glargine represents an ~~economic~~ treatment  
28 option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at  
29 least as effective glycemic control as NPH insulin, and to be cost effective in a range of  
30 countries and settings.[33-39]

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34 Basal insulin analogs have been shown to have several advantages compared to NPH  
35 insulin, including less pharmacologic variability, lower risk of hypoglycemia, and greater  
36 impact on quality of life.[14-16, 20, 21, 40] The rates of hypoglycemia-related events were,  
37 however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is  
38 associated with less hypoglycemia than NPH insulin,[45,20] the switch from NPH insulin to  
39 insulin glargine may usually be considered in patients with evidence of hypoglycemia or  
40 increasing incidence of hypoglycemic events. The baseline hypoglycemic event results  
41 between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort  
42 in the present analysis may be skewed to patients with lower NPH insulin-related  
43 hypoglycemia than expected.

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49 The increased persistence associated with insulin glargine, as shown in this study, may lead  
50 to better clinical outcomes,[41] and potentially improve work-related outcomes.[43, 12, 19,  
51 20, 23] Diabetes-related disability has been shown to result in loss of work-place  
52 productivity.[42-46] In this study, we observed fewer short-term disability days in patients on  
53 insulin glargine, compared with those on NPH insulin. Although the differences were not  
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7 statistically significant, this finding may suggest that initiation of therapy with insulin glargine  
8 could help increase workplace productivity among employed patients with T2DM compared  
9 with those initiating with NPH insulin.  
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12 As with all retrospective studies, issues of sampling bias should be taken into account when  
13 interpreting these results, which may introduce selection bias. The use of PSM methodology  
14 in this study should have helped reduce the impact of selection bias ~~such as confounding by~~  
15 ~~indication~~. In fact, three different matching ratios were tested, and all yielded similar findings.  
16 However, ~~the PSM~~ likely limited patients in the insulin glargine cohort to those most similar to  
17 the NPH insulin cohort and not to those patients with T2DM who use insulin in general.  
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19 Further, some insulin patients may have been missed due to the availability of 90-day/mail  
20 order prescriptions resulting in ~~them~~ their being missed during the 3-month baseline period.  
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24 This study has several limitations. Although the MarketScan data represent a large diverse  
25 population, ~~the study~~ only included information from mainly large, self-insured employers,  
26 whose employees were more likely to be located in certain geographic areas than the  
27 general employee population, and the analysis included ~~an~~ convenience sample of patients  
28 whose employer supplied productivity data. Therefore, this study should not be assumed ~~as~~  
29 to be representative of the overall US population. As with any retrospective observational  
30 study, causality of treatment effects cannot be established in this study. Although the PSM  
31 method was used to balance differences between the two groups included in the study,  
32 confounding by indication or prognosis may still have affected the outcomes observed. The  
33 use of PSM to reduce the treatment selection bias issues such as confounding by  
34 indications, it also led to a significant reduction in the sample size, particularly ~~on~~ in the GLA  
35 insulin glargine group, due to the required matching ratios, and relatively a much smaller  
36 sample size in the NPH group. This may also ~~make~~ the study underpowered to detect all  
37 significant differences between treatment groups. In addition, the similar rate of  
38 hypoglycemia observed between groups is inconsistent with existing literature, as previous  
39 studies suggest a lower risk of hypoglycemia with insulin glargine, compared with NPH  
40 insulin.<sup>[915, 33]</sup> It is unlikely that rates of hypoglycemia would be captured with the same  
41 level of sensitivity in this retrospective analysis as they would in a randomized clinical trial.  
42 Moreover, the low overall hypoglycemia rate in both cohorts may have resulted in insufficient  
43 statistical power to detect significant differences. Coding issues in the claim data may also  
44 have contributed to the lack of statistical robustness. The ~~daily units of insulin (DACON)~~ was  
45 measured based on pharmacy claim data and may not be accurate. For example, patients  
46 on a low dose are instructed to discard unused insulin (particularly in vials) after  
47 approximately 1 month; ~~hence,~~ hence, pharmacy claim data can lead to an overestimation of  
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7 DACON. However, this is unlikely to affect ~~GLA and NPH~~the study groups disproportionately  
8 because they were similar in proportion of patients using insulin pens (~~Table table~~ 2). A1C  
9 data were not available, so neither the effectiveness of glycemic control nor the association  
10 with hypoglycemia could be assessed. Finally, the 12--month follow-up period of this study  
11 may not have been sufficient to detect benefits due to improved persistence and adherence.  
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#### 14 **CONCLUSION**

15 This study showed that insulin glargine resulted in better persistence and adherence, with  
16 lower health care utilization, at similar total healthcare costs despite higher drug-related  
17 costs, than NPH insulin. Better persistence and adherence may lead to long-term health  
18 benefits and additional benefits to patients with T2DM and their employers. Due to the  
19 retrospective nature of this study, further studies need to be conducted to confirm these  
20 findings.  
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#### 24 **ACKNOWLEDGEMENTS**

25 This study was funded by sanofi-aventis U.S., Inc. The authors received editorial and writing  
26 support in the preparation of this manuscript from Ewen Legg, PhD, of Excerpta Medica.  
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#### 30 **DISCLOSURES**

31 LW, LX, and OB: Employees of STATinMED Research, under contract with sanofi-aventis  
32 U.S.  
33

34 RM and WW: Employees of sanofi-aventis U.S.  
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#### 38 **CONTRIBUTIONS**

39 LW: Active in study design, statistical plan, data analysis, drafting, and review of manuscript.

40 WW: Active in creating the concept and study design, drafting, and review of manuscript.

41 RM: Active in creating the concept and study design, drafting, and review of manuscript.

42 LX: Role in statistical analysis and review of manuscript.

43 OB: Active in creating the study design, statistical plan, and review of manuscript.  
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#### 47 **DATA SHARING**

48 Additional data ~~is-are~~ available by e-mailing Dr Onur Baser obaser@statinmed.com  
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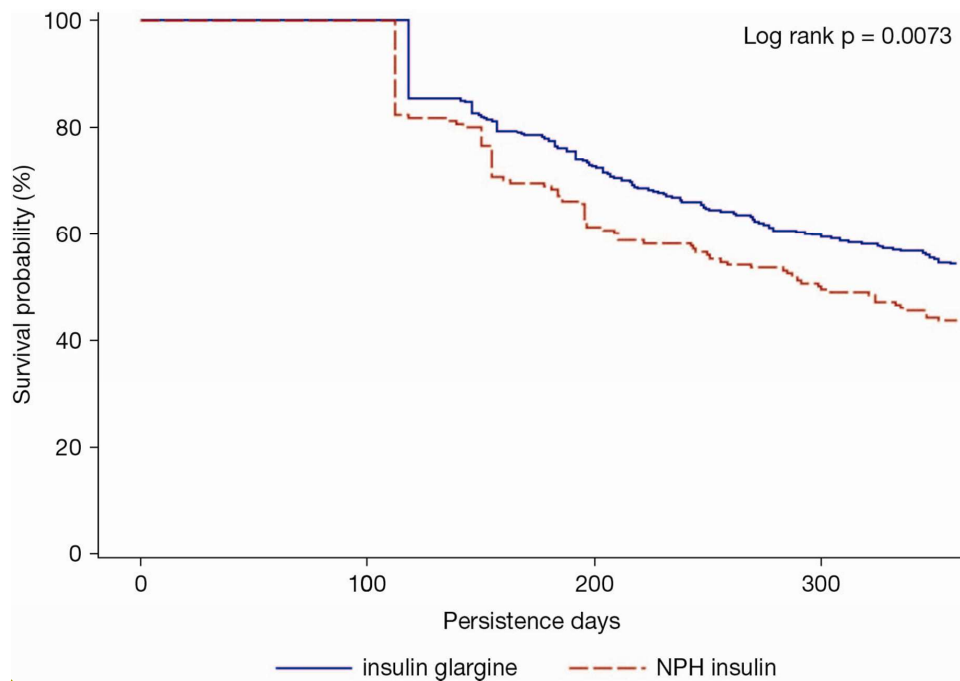
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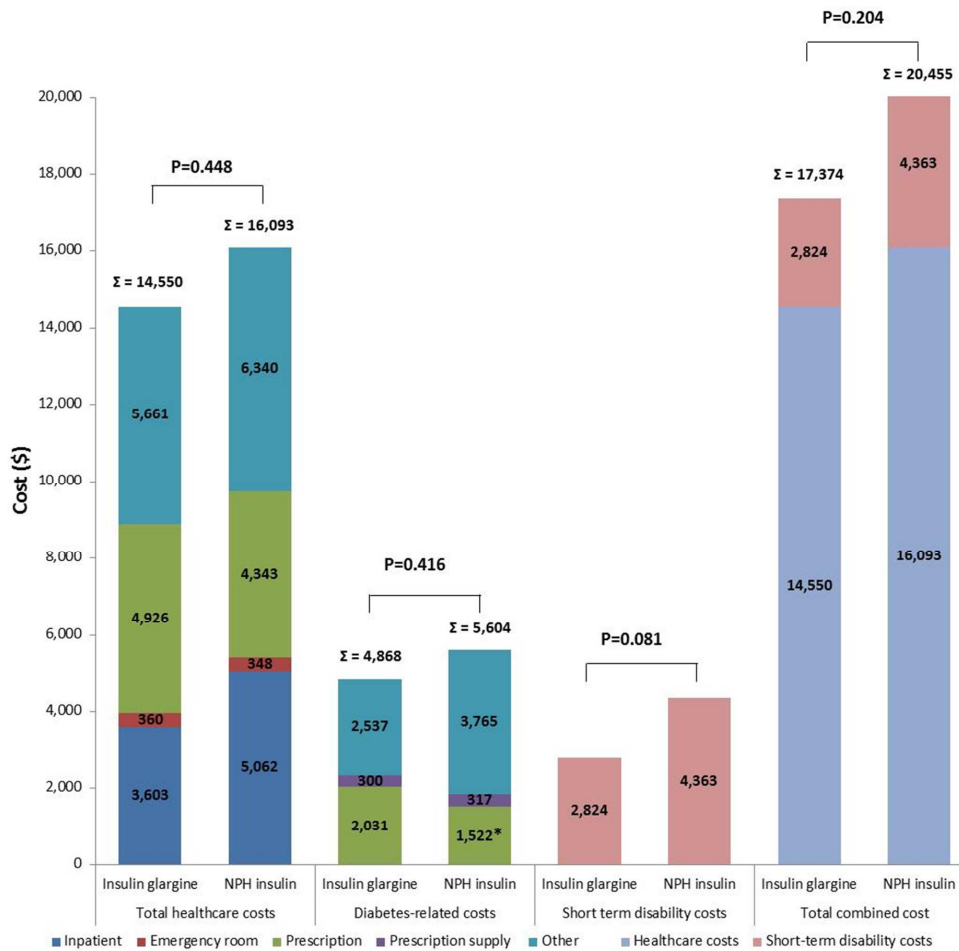
**Figure 1** Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine and NPH insulin



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**Figure 2** 1-year short-term disability and direct healthcare costs. (Total between-group differences did not reach statistical significance).



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\*P<0.0001 vs insulin glargine

**Figure legends**

**Figure 1** Persistence (90th percentile) and adherence with insulin therapy: 1 year follow up.

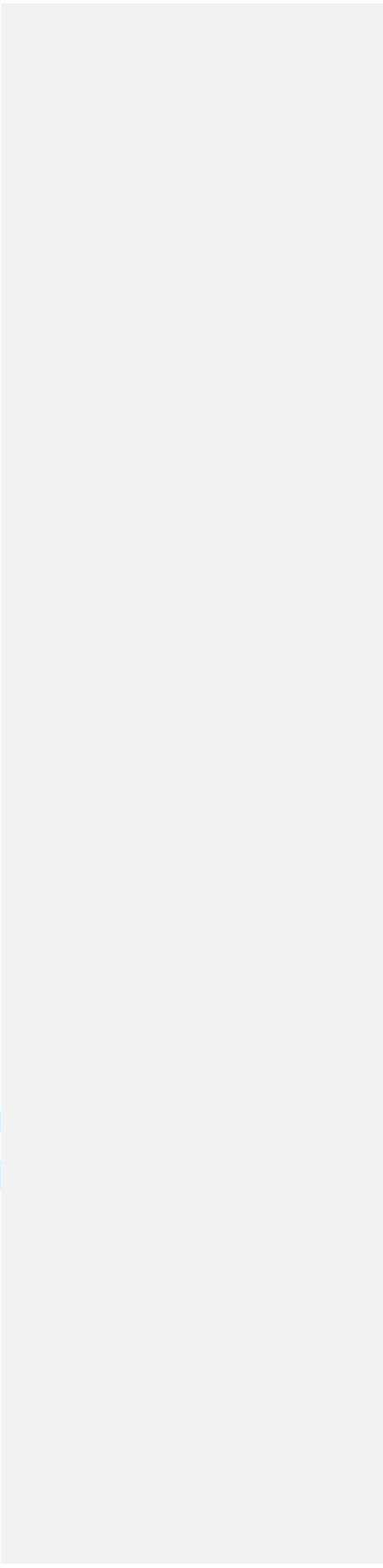
\*P<0.05 vs insulin glargine

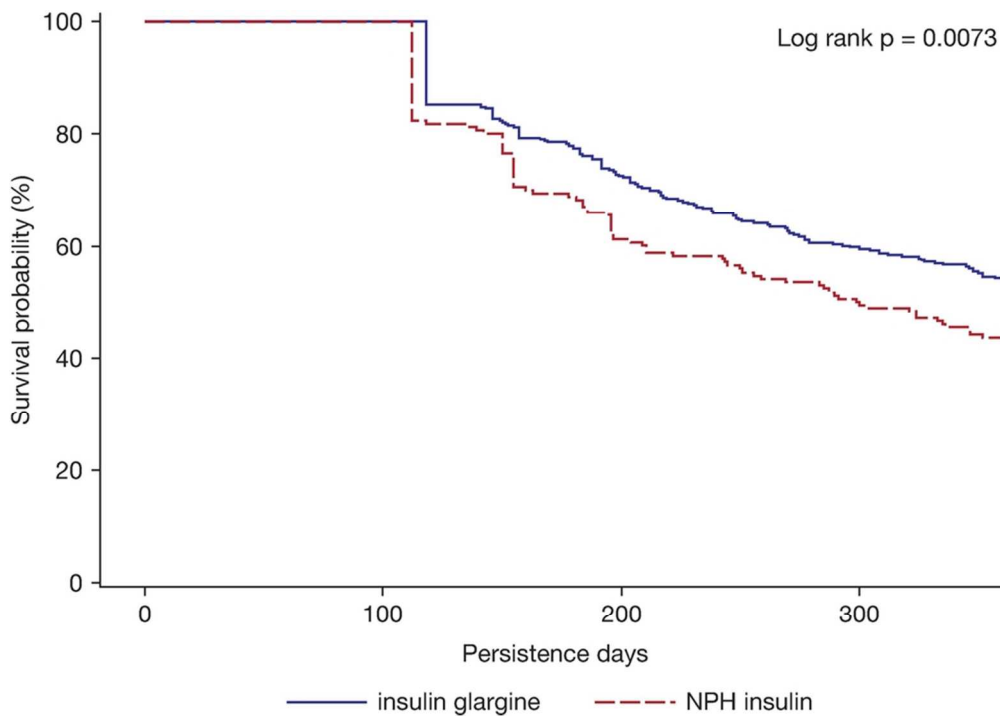
**Figure 2** Kaplan-Meier Curve of follow up 1 Year year persistence days between insulin glargine and NPH insulin

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~~Figure 3 2~~ 1-year short term disability and direct healthcare costs. (Total between group differences did not reach statistical significance).  
\*P<0.0001 vs insulin glargine

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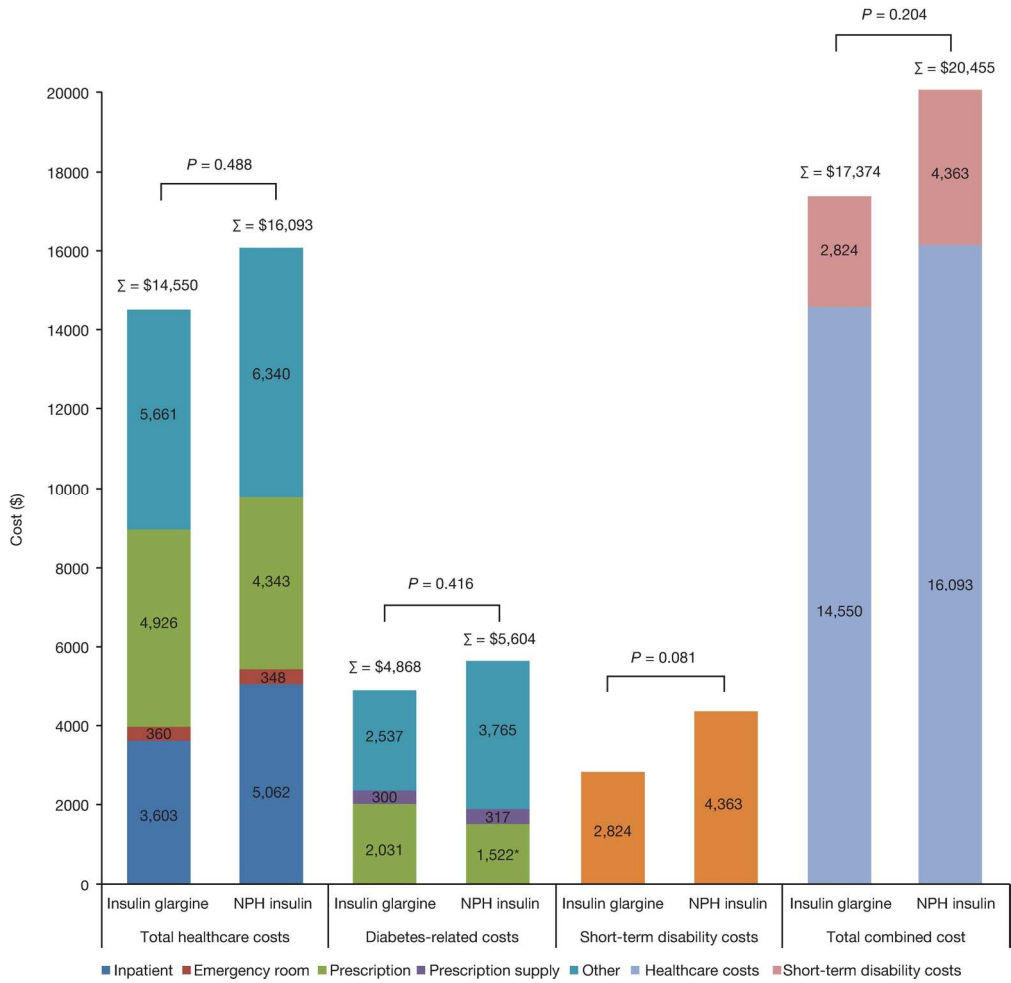




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57  
58  
59  
60



181x175mm (300 x 300 DPI)

only