BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002348
Article Type:	Research
Date Submitted by the Author:	14-Nov-2012
Complete List of Authors:	Wang, Li; STATinMED Research, Wei, Wenhui; sanofi-aventis US, Miao, Raymond; sanofi-aventis US, Xie, Lin; STATinMED Research, Baser, Onur; STATinMED Research, ; The University of Michigan,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics
Keywords:	healthcare utilization, employee productivity, diabetes costs

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

Corresponding author

Onur Baser

STATinMED Research

211 N. 4th Ave

Ann Arbor, MI 48104

Cell: (734) 646-7991

Work: (734) 222-5426

Fax:(734) 864-0359

Authors

Li Wang[1], Wenhui Wei[2], Raymond Miao[2], Lin Xie[1], Onur Baser[1,3]

1. STATinMED Research, Ann Arbor, MI, USA
2. sanofi-aventis US, Bridgewater, NJ, USA
3. The University of Michigan, Ann Arbor, MI, USA

Word count: 3,346

Article Summary

Aritcle 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).

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

INTRODUCTION

In the Unites States (US), diabetes affects an estimated 25.8 million people (8.3% of the US population).[1] Type 2 diabetes mellitus (T2DM) accounts for substantial clinical sequelae, including microvascular and macrovascular complications,[1] and leads to significant direct and indirect costs associated with treatment and lost productivity. Furthermore, T2DM imposes an important economic burden to self-insured employers.[2] People with diabetes incur more medical costs, have more frequent physician encounters and use more medical services than people without diabetes.[3] In 2007, approximately 1 in 5 healthcare dollars in the US was spent caring for people with diabetes, and T2DM in the US incurred costs estimated at $174 billion.[4] Of this total, direct medical costs comprised an estimated $116 billion, while indirect costs – including treating the consequences of inadequate glycemic control and other complications of diabetes – were estimated at $58 billion.[4]

Diabetes-related costs to employees and employers are associated with disability and reduced productivity, work loss, and associated comorbidities.[5, 6] In one survey, the impact of diabetes-associated disability in the US, in terms of aggregate losses, was estimated at $9.3 billion in a single year (1994).[7] Similarly, a longitudinal cohort study reported estimated costs to employers and employees in lost productivity in the US of $7.3 billion annually, and $58.6 billion in total over an 8-year period (1992–2000). This figure included $31.7 billion due to disability, $4.4 billion in lost income due to early retirement, $0.5 billion due to sick days, and $22 billion due to premature mortality.[8] In addition, the micro- and macrovascular complications associated with diabetes contribute further to the overall costs and productivity reductions. Macrovascular comorbidities are associated with additional costs of $5,120, 13.03 missed workdays, and 7.60 bed days per patient, and the marginal lost productivity cost has been estimated at $2,388 annually per patient.[9] With regard to microvascular complications, diabetic retinopathy resulted in significantly higher costs for affected employees (annual direct and indirect costs of $18,218 and $3,548, respectively), compared with employees with diabetes but no retinopathy ($11,898 and $2,374).[10] In addition, for specific populations at high risk of diabetes, the condition predicts absenteeism among obese and morbidly obese workers.[11] Overall, reduced national productivity related to diabetes accounted for $58 billion in 2007 in the US.[4]

A regimen of oral glucose-lowering drugs combined with basal insulin analogs provides clinically relevant improvements in glycemic control with a good safety profile.[12] In addition, early improvements in glucose control can reduce the long-term risk of macrovascular events associated with T2DM, as well as reduce microvascular complications.[13] Options for basal insulin include insulin glargine, a once-daily, long-acting basal insulin analog, or Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting insulin, typically administered once or twice daily. 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.[14-16] Notably, hypoglycemia contributes considerably to the costs of diabetes. In a recent study of 2,664 employees, the annualized cost of hypoglycemia was $3,241; moreover, patients with hypoglycemia experienced 77% more short-term disability annually than those without.[17]

Simplicity of treatment regimen is important for those transitioning from oral to insulin therapy. The once-daily regimen provided by insulin glargine may also have implications for increased patient persistence and adherence[18] and, consequently, may improve outcomes. 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] Reasons given for diabetes patients missing insulin doses include: needing more daily injections, injections interfering with daily activities, and embarrassment.[20] Such considerations, in relation to convenience and adherence, may be particularly important for working people who have T2DM. In reality, patients taking insulin glargine have been shown to be more likely to persist with their medication than those taking NPH insulin.[21]

Successful treatment, including adherence to medication, is key to the improvement of outcomes for employees. Better adherence to diabetes medication is associated with improved glycemic control and decreased healthcare resource utilization.[22] In addition, because adherence to medication reduces the incidence of complications, it is associated with improved work-related outcomes, such as reducing the number of short-term disability days.[23] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[24-25] 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.[26] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[24,27]

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

METHODS

Database

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

Cohort selection criteria

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

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

Categories of healthcare resource utilization included numbers of outpatient visits, emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare 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),[31] which amounts to $168, since disability programs typically pay for 70% of lost income.[32]

Total cost

Total cost was assessed by combining direct costs (healthcare) 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 remove the observed baseline selection bias between the two study cohorts, propensity score matching (PSM) methodology[33] was implemented, with a stringent 2:1 matching of patients initiating insulin glargine or NPH insulin. Propensity scores for initiating insulin glargine vs 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.

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
Gender, female (%)	153 (42.9%)	81 (45.5%)	0.5789
Age, years, mean ± SD	49 ± 10	49 ± 10	0.7580
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%)	
Pen use, n (%)	59 (16.5%)	33 (18.5%)	
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 (%)			
Obesity	5 (1.4)	4 (2.2)	0.4758
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
Congestive heart failure	12 (3.3)	4 (2.2)	0.4728
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
Total healthcare utilization, n (%) or mean ± SD			
Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
Total hospitalization days	0.97 ± 3.38	0.72 ± 2.11	0.3018
ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	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
Diabetes-related healthcare utilization, n (%) or mean ± SD			
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
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean ± SD			
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
Total diabetes-related healthcare cost, mean ± SD			
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
Co-pay, 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 ± 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

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
Persistence/adherence, n (%) or mean ± SD			
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
Hypoglycemia, n (%) or mean ± SD			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
Total healthcare utilization, n (%) or mean ± SD			
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
Diabetes-related healthcare utilization, n (%) or mean ± SD			
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
Loss in productivity, mean ± SD			
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%;

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

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 0.36 per patient per year in the insulin glargine group, compared with 0.38 in the NPH insulin group (P=0.7944). However, the total number of short-term disability days and the associated cost were marginally 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 3).

In terms of combined total costs, a non-significant difference in favor of insulin glargine patients was evident ($17,374for GLA vs $20,455for NPH, P=0.204).

Correlations

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

Sensitivity analysis

The sensitivity analyses using 1:1 and 3:1 PSM yielded similar results overall. 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 $2,173vs $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, GLA, *n*=160, NPH) 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 fewer hospitalizations and lower inpatient costs associated with the use of insulin glargine, compared with NPH insulin. In regard to short-term disability in both primary and sensitivity analyses, marginally fewer short-term disability days and lower associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort. It is likely that the reduction of short-term disability are related to fewer hospitalizations in the insulin glargine cohort. Indeed, the correlation analysis showed that patients with any hospitalizations were significantly more likely to claim for short-term disability: both the number and duration of hospitalizations were highly correlated with the number of claims and the duration of short-term disability.

A variety of studies comparing economic outcomes of insulin glargine and NPH insulin in patients with T2DM have indicated that insulin glargine represents a cost-effective treatment option, compared with NPH insulin. Once-daily insulin glargine has been shown to provide at least as effective glycemic control as NPH insulin, and to be cost effective in a range of countries and settings.[34-40]

Basal insulin analogs, such as insulin glargine, have been shown to have several advantages compared to NPH insulin including less pharmacologic variability, lower risk of hypoglycemia, and greater impact on quality of life.[41] The increased adherence associated with insulin glargine, as shown in this study, may lead to better clinical outcomes and potentially improve work-related outcomes.[22, 23, 26] Diabetes-related disability has been shown to result in loss of work place productivity;[42-46] In this study, we observed fewer short-term disability days in patients on insulin glargine, compared with those on NPH insulin, although the difference was not statistically significant in all analysis. This finding

suggests that initiation of therapy with insulin glargine may help increase workplace productivity among employed patients with T2DM.

As with all retrospective studies, issues of sampling bias should be taken into account when interpreting these results. However, the use of PSM methodology in this study should reduce the impact of any such bias. Causality of treatment effects cannot be established in this study. Although the MarketScan Database represents a large diverse data source, it should not be assumed that the sample obtained is representative of the overall US population. Furthermore, the similar rate of hypoglycemia is inconsistent with existing literature, as previous evidence suggests a lower risk of hypoglycemia with insulin glargine, compared with NPH insulin in previous studies.[14, 34] It is unlikely that rates of hypoglycemia would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Further, the low overall hypoglycemia rate in both cohorts, may have resulted in insufficient statistical power to detect significant differences. Coding issues in the claim data may also have contributed to the lack of statistical robustness. Finally, A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia, could be assessed.

CONCLUSION

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

ACKNOWLEDGEMENTS

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

DISCLOSURES

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

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

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.

FUNDING STATEMENT

Funded by This study was funded by sanofi-aventis U.S., Inc.

References

1. **US Centers for Disease Control and Prevention**. National diabetes fact sheet 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed 18 June 2012.
2. **Durden ED**, Alemayehu B, Bouchard JR, *et al*.. Direct health care costs of patients with type 2 diabetes within a privately insured employed population, 2000 and 2005. *J Occup Environ Med* 2009;**51**:1460–5.
3. **Rendell M**, Kimmel DB, Bamisedun O, *et al*. The healthcare status of the diabetic population as reflected by physician claims to a major insurer. *Arch Intern Med* 1993;**153**:1360–6.
4. **American Diabetes Association**. *Diabetes Care* 2008;**31**:596–615.
5. **Morsanutto A**, Berto P, Lopatriello S, *et al.* Major complications have an impact on total annual medical cost of diabetes: results of a database analysis. *J Diabetes Complications* 2006;**20**:163–9.
6. **Kim S**. Burden of Hospitalizations primarily due to incontrolled diabetes: implications of inadequate primary healthcare in the United States. *Diabetes Care* 2007;**30**:1281–2.
7. **Yassin AS**, Beckles GL, Messonnier ML. Diabetes and its economic impact among adults with diabetes. *J Occup Environ Med* 2002;**44**:136–42.
8. **Vijan S**, Hayward RA, Langa KM. The impact of diabetes on workforce participation: results from a National household sample. *Health Serv Res* 2004;**39**:1653–70.
9. **Fu AZ**, Qiu Y, Radican L, Wells BJ. Health care and productivity costs associated with diabetic patients with macrovascular comorbid conditions. *Diabetes Care* 2009;**32**:2187–92.
10. **Lee LJ**, Yu AP, Cahill KE, *et al.* Direct and indirect costs among employees with diabetic retinopathy in the United States. *Curr Med Res Opin* 2008;**24**:1549–59.
11. **Cawley J**, Rizzo JA, Haas K. The association of diabetes with job absenteeism costs among obese and morbidly obese workers. *J Occup Environ Med* 2008 May;**50**:527–34.

12. **Rosenstock J**, M. Davies, Home PD, *et al.* A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;**51**:408–16.
13. **Mattila TK**, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010;**70**:2229–45.
14. **Rosenstock J**, Dailey G, Massi-Benedetti M, *et al*. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;**28**:950–5.
15. **Mullins P**, Sharplin P, Yki-Järvinen H, *et al*. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;**29**:1607–19.
16. **Home PD**, Fritsche A, Schinzel S, Massi-Benedetti M. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;**12**:772–9.
17. **Rhoads GG**, Orsini LS, Crown W, *et al.* Contribution of hypoglycemia to medical care expenditures and short-term disability in employees with diabetes. *J Occup Environ Med* 2005;**47**:447–52.
18. **Riddle MC**. Making the transition from oral to insulin therapy. *Am J Med* 2005;**118(**suppl 5A):14S–20S.
19. **Jansà M**, Hernández C, Vidal M, *et al*. Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. *Patient Educ Couns* 2010;**81**:161–8.
20. **Peyrot M**, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. *Diabetes Care* 2010;**33**:240–5.

21. **Cooke CE**, Lee HY, Tong YP, Haines ST. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr Med Res Opin* 2010;**26**:231–8.
22. **Asche C**, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;**33**:74–109.
23. **Gibson TB**, Song X, Alemayehu B, Wang SS, Waddell JL, Bouchard JR, Forma F. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care* 2010;**16**:589–600.
24. **Sokol MC**, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–30.
25. **Stuart B**, Davidoff A, Lopert R, *et al*. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health Serv Res* 2011;**46**:1180–99.
26. **Sprince NL**, Pospisil S, Peek-Asa C. Occupational injuries among workers with diabetes: the National Health Interview Survey, 1997–2005. *J Occup Environ Med* 2008;**50**:804–8.
27. **Rizzo JA**, Abbott TA, Pashko S. Labour productivity effects of prescribed medicines for chronicall ill workers. *Health Econ* 1996;**5**:249–65.
28. **Davis SN**, Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract* 2011;**17**:845–52.
29. **Baser O**, Bouchard J, DeLuzio T, *et al*. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;**27**:94–104.
30. **Zhao Y**, Campbell CR, Fonseca V, Shi L Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* 2012;**35**:1126–32.

31. **Goetzel RZ**, Long SR, Ozminkowski RJ, *et al*. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.
32. **Hawkins K**, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *J Occup Environ Med* 2007;**49**:368–74.
33. **Rosenbaum PR**, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
34. **Rhoads GG**, Dain MP, Zhang Q, Kennedy L. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. *Diabetes Obes Metab* 2011;**13**:711–7.
35. **Clissold R**, Clissold S. Insulin glargine in the management of diabetes mellitus: an evidence-based assessment of its clinical efficacy and economic value. *Core Evid* 2007**;2**:89–110.
36. **Grima DT**, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics* 2007;**25**:253–66.
37. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. *Int J Clin Pharmacol Ther* 2007;**45**:203–20.
38. **Schöffski O**, Breitscheidel L, Benter U, *et al*. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;**11**:695–712.
39. **Lee LJ**, Yu AP, Johnson SJ, *et al*. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pract* 2010;**87**:108–16.

40. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther* 2011;**49**:217–30.
41. **Hartman I**. Insulin analogs: impact on treatment success, satisfaction, quality of life and adherence. *Clin Med Res* 2008;**6**:54–67.
42. **Gore M**, Brandenburg NA, Hoffman DL, *et al*. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006;**7**:892–900.
43. **Musich S**, Hook D, Baaner S, Edington DW. The association of two productivity measures with health risks and medical conditions in an Australian employee population. *Am J Health Promot* 2006;**20**:353–63.
44. **Sullivan PW**, Ghushchyan V, Wyatt HR, *et al*. Productivity costs associated with cardiometabolic risk factor clusters in the United States. *Value Health* 2007;**10**:443–50.
45. **Sullivan PW**, Ghushchyan V, Ben-Joseph RH. The effect of obesity and cardiometabolic risk factors on expenditures and productivity in the United States. *Obesity (Silver Spring)* 2008;**16**:2155–62.
46. **Kannan H**, Thompson S, Bolge SC. Economic and humanistic outcomes associated with comorbid type-2 diabetes, high cholesterol and hypertension among individuals who are overweight or obese. *J Occup Environ Med* 2008;**50**:542–9.

Figure legends

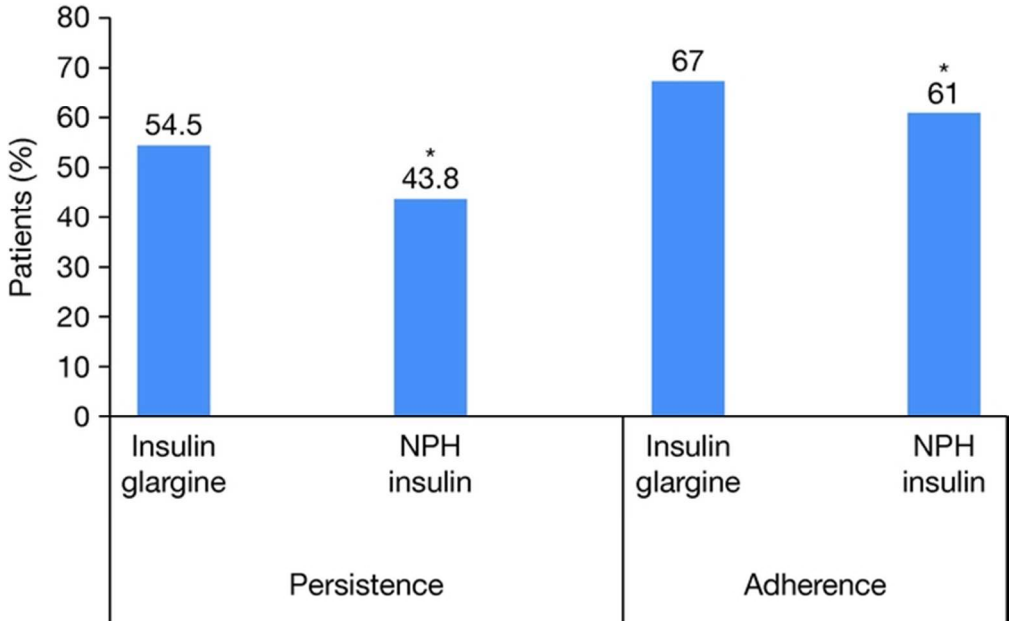
Figure 1 Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

*P<0.05 vs insulin glargine

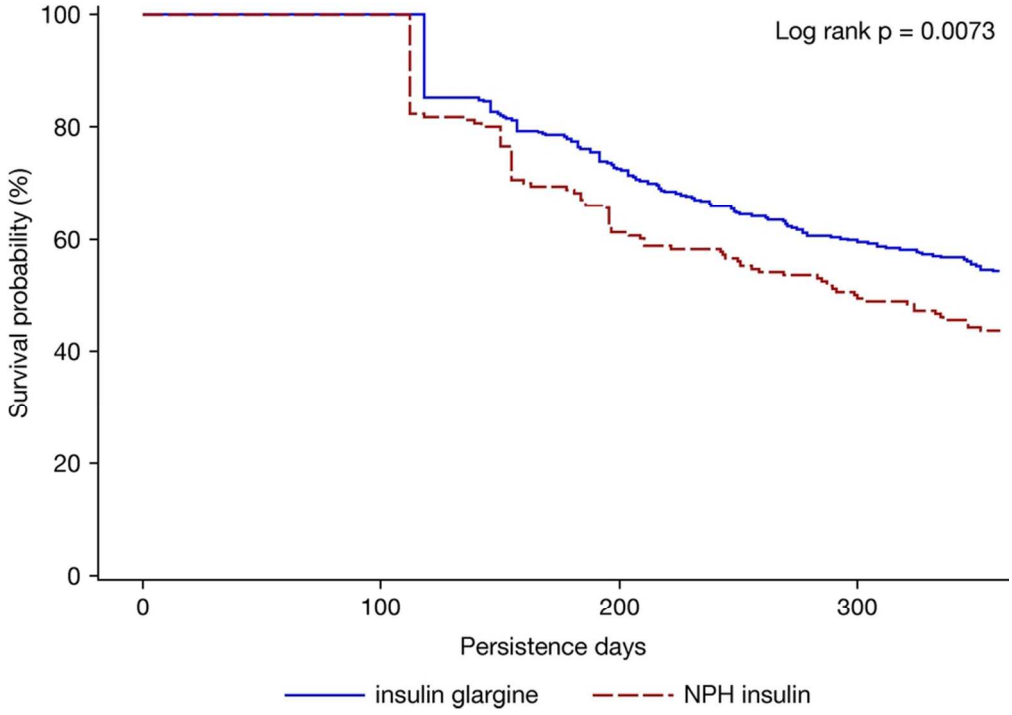
Figure 2 Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine and NPH insulin

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

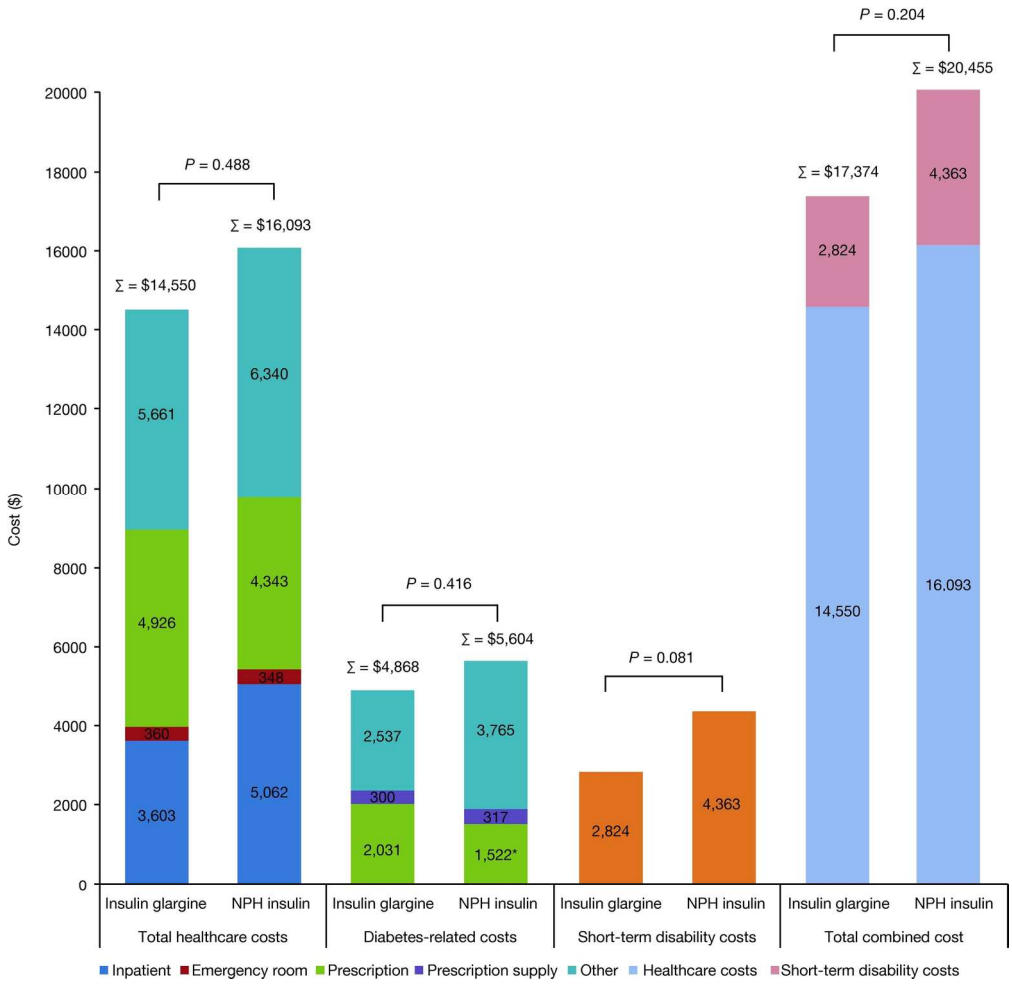
*P<0.0001 vs insulin glargine



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



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



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

	Study Section	Additional Remarks
Study Design		
(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	
Data Collection		
(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	
Analysis and Interpretation of Results		
(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	

	Study Section	Additional Remarks
(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	

BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002348.R1
Article Type:	Research
Date Submitted by the Author:	04-Mar-2013
Complete List of Authors:	Wang, Li; STATinMED Research, Wei, Wenhui; sanofi-aventis US, Miao, Raymond; sanofi-aventis US, Xie, Lin; STATinMED Research, Baser, Onur; STATinMED Research, ; The University of Michigan,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics
Keywords:	healthcare utilization, employee productivity, diabetes costs

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

Corresponding author

Onur Baser

STATinMED Research

211 N. 4th Ave

Ann Arbor, MI 48104

Cell: (734) 646-7991

Work: (734) 222-5426

Fax:(734) 864-0359

Authors

Li Wang[1], Wenhui Wei[2], Raymond Miao[2], Lin Xie[1], Onur Baser[1,3]

1. STATinMED Research, Ann Arbor, MI, USA
2. sanofi-aventis US, Bridgewater, NJ, USA
3. The University of Michigan, Ann Arbor, MI, USA

Word count: 3,158

Article Summary

Aritcle 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 biasbetween 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-tem-disability coverages .

Design: Retrospective cohort study

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

Participants: Adult employees wi+th 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

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

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

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

who are adherent to medication.[23] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[21, 24]

Although there are data in support of the clinical benefits of basal insulins there is currently a paucity of real-world information about the impact of different basal insulin regimens on healthcare utilization, employee disability, and their associated costs from an employer's perspective.

METHODS

Database

This study is a retrospective analysis from the employer perspective, of patients' medical and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters Database 2003–2009. This database captures person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services from about 100 large employers, health plans, and government and public organizations.

Short-term disability data were extracted from the MarketScan Health and Productivity Management Database, which is an integrated database that contains information on absence, short-term disability, and workers' compensation experience. This information is linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial Claims and Encounters Database for these employees, providing a unique and valuable resource for examining health and productivity issues for an employed, privately insured population.

The MarketScan Research Databases are fully compliant with the letter and spirit of the Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board review was waived.

Cohort selection criteria

Included in the analysis were employees, but not their dependents, of 18 years of age or older with T2DM, defined as having made at least one inpatient visit or two physician visits dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine or NPH insulin with the date of the first such claim being the index date (prescriptions of

other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare benefits and work benefits for short-term disability for 3 months prior to insulin initiation (baseline period), and 12 months after insulin initiation (follow-up period); and on at least one oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The patient cohorts for comparison were determined on the basis of use of insulin glargine or NPH insulin at initiation of insulin therapy. Outcomes were compared between the matched cohorts after 1 year of follow-up.

Baseline characteristics

Data were analyzed to assess baseline characteristics, including: gender; age; OAD use; comorbidities; healthcare utilization/costs; and short-term disability for 3 months prior to insulin initiation for all patients. 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 previously published studies,[25-27] 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. For example, our analysis showed that for patients who filled prescription for 10 mL and refilled later, 90% of GLA patients refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered discontinuing GLA if he/she previously filled a prescription for 10mL of GLA but did not refill it within 119 days. 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 [28] (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) to correct the issue that almost all prescriptions are dispensed with a 30-day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in

the analysis period divided by the number of days in the analysis period) by the average number of days between insulin study drug prescription refills for patients using the insulin divided by the average days' supply for patients using the insulin. By using data based on the actual gap between the days' supply and the days to next refill, this adjustment is necessary to measure real adherence to doctor's instructions.

Clinical outcomes

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).[29] Daily average consumption (DACON) of insulin was estimated based on pharmacy claim data and calculated as the total number of units dispensed before the last refill of study drug divided by the total number of days between initiation and last refill during follow-up period. A1C data were not available in this study.

Healthcare resource utilization and cost

Categories of healthcare resource utilization included numbers of outpatient visits, emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare 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),[30] which amounts to $168, since disability programs typically pay for 70% of lost income.[31]

Total cost

Total cost was assessed by combining direct costs (healthcare) 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 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 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 the 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. Before the matching, GLA patients were more likely to be male, older, using insulin pen, and had higher copayment than NPH patients (data not shown here), indicating confounding by indication as selection bias. The 2:1 PSM yielded a total of 534 patients (GLA: 356; NPH 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
Insulin Pen use, n (%)	59 (16.5%)	33 (18.5%)	
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 (%)			
Obesity	5 (1.4)	4 (2.2)	0.4758
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
Congestive heart failure	12 (3.3)	4 (2.2)	0.4728
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
Total healthcare utilization, n (%) or mean ± SD [median]			
Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]	0.3018
ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	25 (14.0%)	0.2550
Hospitalization/patient	0.16 ± 0.39 [0]	0.17 ± 0.42 [0]	0.6458
ER visits/patient	0.31 ± 0.67 [0]	0.28 ± 0.68 [0]	0.6817
Endocrinologist visits/patient	0.15 ± 0.48 [0]	0.19 ± 0.55 [0]	0.3844
Diabetes-related healthcare utilization, n (%) or mean ± SD [median]			
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]	0.11 ± 0.34 [0]	0.5570
Endocrinologist visits/patient	0.14 ± 0.47 [0]	0.17 ± 0.53 [0]	0.4951
Office visits/patient	1.74 ± 1.43 [1]	1.60 ± 1.44 [1]	0.2782
Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]	0.4975
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]	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

		Insulin glargine (n=356)	NPH insulin (n=178)	P value
Total diabetes-related healthcare cost, mean ± SD [median]	Total cost	5259 ± 14237 [1632]	4794 ± 10731 [1895]	0.6735
	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 (%)				0.8694
	$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 ± 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
Hypoglycemia, n (%) or mean ± SD			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
Total healthcare utilization, n (%) or mean ± SD			
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
Diabetes-related healthcare utilization, n (%) or mean ± SD			
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
Loss in productivity, mean ± SD			
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

costs for the insulin glargine cohort ($2,031), compared with the NPH insulin cohort ($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 0.36 per patient per year in the insulin glargine group, compared with 0.38 in the NPH insulin group (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 3). Combined total costs were similar between the insulins ($17,374 for GLA vs $20,455 for NPH, P=0.204).

Correlations

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 and 3:1 PSM yielded similar results overall. 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 $2,173vs $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 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations and endocrinologist visits were also numerically lower in GLA group but not statistically significant, probably due to sample size and the inaccuracy of using ICD-9-CM diagnosis code (250.xx) to capture diabetes-related events. In regard to short-term disability in both primary and sensitivity analyses, numerically fewer short-term disability days and lower associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort, but this was not significant. It is likely that the reduction in short-term disability is related to fewer hospitalizations in the insulin glargine cohort. Indeed, the correlation analysis showed that patients with any hospitalizations were significantly more likely to claim for short-term disability: both the number and duration of hospitalizations were highly correlated with the number of claims and the duration of short-term disability.

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

Basal insulin analogs have been shown to have several advantages compared to NPH insulin including less pharmacologic variability, lower risk of hypoglycemia, and greater impact on quality of life.[14-16, 40] The rates of hypoglycemia-related events were, however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated with less hypoglycemia than NPH insulin,[15] the switch from NPH insulin to insulin glargine may usually be considered in patients with evidence of hypoglycemia or increasing incidence

of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort in the present analysis may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.

The increased persistence associated with insulin glargine, as shown in this study, may lead to better clinical outcomes,[41] and potentially improve work-related outcomes.[13, 20, 23] Diabetes-related disability has been shown to result in loss of work place productivity.[42-46] In this study, we observed fewer short-term disability days in patients on insulin glargine, compared with those on NPH insulin. Although the differences were not statistically significant, this finding may suggest that initiation of therapy with insulin glargine could help increase workplace productivity among employed patients with T2DM compared with those initiating with NPH insulin.

As with all retrospective studies, issues of sampling bias should be taken into account when interpreting these results, which may introduce selection bias. The use of PSM methodology in this study should have helped reduce the impact of selection bias such as confounding by indication. In fact, three different matching ratios were tested, and all yielded similar findings. However, it likely limited patients in the insulin glargine cohort to those most similar to the NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further, some insulin patients may have been missed due to the availability of 90 day/mail order prescriptions resulting in them being missed during the 3 month baseline period.

This study has several limitations. Although the MarketScan data represent a large diverse population, it only included information from mainly large, self-insured employers, whose employees were more likely to locate in certain geographic areas than the general employee population, and the analysis included an convenience sample of patients whose employer supplied productivity data. Therefore, this study should not be assumed as representative of the overall US population. As any retrospective observational study, causality of treatment effects cannot be established in this study. Although the PSM method was used to reduce the treatment selection bias issues such as confounding by indications, it also led to significant reduction in the sample size, particularly on the GLA group, due to the required matching ratios, and relatively much smaller sample size in NPH group. This may also makes the study underpowered to detect all significant differences between treatment groups. In addition, the similar rate of hypoglycemia observed between groups is inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia with insulin glargine, compared with NPH insulin.[9, 33] It is unlikely that rates of hypoglycemia would be captured with the same level of sensitivity in this retrospective

analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia rate in both cohorts may have resulted in insufficient statistical power to detect significant differences. Coding issues in the claim data may also have contributed to the lack of statistical robustness. The daily units of insulin (DACON) was measured based on pharmacy claim data and may not be accurate. For example, patients on a low dose are instructed to discard unused insulin (particularly in vials) after approximately 1 month, hence, pharmacy claim data can lead to an overestimation of DACON**.** However, this is unlikely to affect GLA and NPH groups disproportionally because they were similar in proportion of patients using insulin pens (Table 2). A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia could be assessed. Finally, the 12 month follow-up period of this study may not have been sufficient to detect benefits due to improved persistence and adherence.

CONCLUSION

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

ACKNOWLEDGEMENTS

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

DISCLOSURES

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

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

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 Baser obaser@statinmed.com

References

1. **US Centers for Disease Control and Prevention**. National diabetes fact sheet 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed 18 June 2012.
2. **Morsanutto A**, Berto P, Lopatriello S, *et al.* Major complications have an impact on total annual medical cost of diabetes: results of a database analysis. *J Diabetes Complications* 2006;**20**:163–9.
3. **Kim S**. Burden of Hospitalizations primarily due to incontrolled diabetes: implications of inadequate primary healthcare in the United States. *Diabetes Care* 2007;**30**:1281–2.
4. **Durden ED**, Alemayehu B, Bouchard JR*, et al*. Direct health care costs of patients with type 2 diabetes within a privately insured employed population, 2000 and 2005. *J Occup Environ Med* 2009;**51**:1460–5.
5. **American Diabetes Association**. *Diabetes Care* 2008;**31**:596–615.
6. **Gillum LA**, Gouveia C, Dorsey ER, *et al.* NIH disease funding levels and burden of disease. *PLoS One*. 2011;**6**:e16837.
7. **Rosenstock J**, M. Davies, Home PD, *et al.* A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;**51**:408–16.
8. **Mattila TK**, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010;**70**:2229–45.
9. **Rosenstock J**, Dailey G, Massi-Benedetti M, *et al.* Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;**28**:950–5.

10. **Mullins P**, Sharplin P, Yki-Järvinen H, *et al*. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;**29**:1607–19.
11. **Home PD**, Fritsche A, Schinzel S, Massi-Benedetti M. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;**12**:772–9.
12. **Riddle MC**. Making the transition from oral to insulin therapy. *Am J Med* 2005;**118(**suppl 5A):14S–20S.
13. Twenty-Four Hour Action of Insulin Glargine (Lantus) May Be too Short for Once-Daily Dosing: A case report
14. **Asche C**, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;**33**:74–109.
15. **Esposito K**, Chiodini P, Caouano A, *et al.* Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes. *Diabetes Care* 2012;**35**:2698–2705,
16. **Inzucchi SE**, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type2 diabetes: a patient-centered approach. *Diabetes Care* 2012;**35**:1364-79.
17. **Esposito K,** Capuano A, Giugliano D. Humalog (lispro) for type 2 diabetes. *Expert Opin Biol Ther* 2012;**12**:1541-50.
18. **Cooke CE**, Lee HY, Tong YP, Haines ST. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr Med Res Opin* 2010;**26**:231–8.
19. **Jansà M,** Hernández C, Vidal M, et al. Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. *Patient Educ Couns* 2010;**81**:161–8.

20. **Gibson TB,** Song X, Alemayehu B, Wang SS, Waddell JL, Bouchard JR, Forma F. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care* 2010;**16**:589–600.
21. **Sokol MC**, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–30.
22. **Stuart B**, Davidoff A, Lopert R, *et al*. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health Serv Res* 2011;**46**:1180–99.
23. **Sprince NL**, Pospisil S, Peek-Asa C. Occupational injuries among workers with diabetes: the National Health Interview Survey, 1997–2005. J Occup Environ Med 2008;**50**:804–8.
24. **Rizzo JA**, Abbott TA, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. *Health Econ* 1996;**5**:249–65.
25. **Davis SN,** Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract* 2011;**17**:845–52.
26. **Xie L,** Wei W, Pan C, et al. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. *Adv Ther* 2011;28: 1000-11.
27. **Xie L,** Zhou S, Wei W et al. Does Pen Help? A Real-World Outcomes Study of Switching from Vial to Disposable Pen Among Insulin Glargine-Treated Patients with Type 2 Diabetes Mellitus. Diabetes Technol Ther 2013 Jan 21. [Epub ahead of print]
28. **Baser O**, Bouchard J, DeLuzio T, *et al*. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;**27**:94–104.
29. **Zhao Y**, Campbell CR, Fonseca V, Shi L Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* 2012;**35**:1126–32.
30. **Goetzel RZ**, Long SR, Ozminkowski RJ, *et al*. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.

31. **Hawkins K**, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *J Occup Environ Med* 2007;**49**:368–74.
32. **Rosenbaum PR,** Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
33. **Rhoads GG**, Dain MP, Zhang Q, Kennedy L. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. *Diabetes Obes Metab* 2011;**13**:711–7.
34. **Clissold R**, Clissold S. Insulin glargine in the management of diabetes mellitus: an evidence-based assessment of its clinical efficacy and economic value. *Core Evid* 2007**;2**:89–110.
35. **Grima DT**, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics* 2007;**25**:253–66.
36. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. *Int J Clin Pharmacol Ther* 2007;**45**:203–20.
37. **Schöffski O**, Breitscheidel L, Benter U, *et al*. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;**11**:695–712.
38. **Lee LJ**, Yu AP, Johnson SJ, *et al*. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pract* 2010;**87**:108–16.
39. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther* 2011;**49**:217–30.

40. **Hartman I.** Insulin analogs: impact on treatment success, satisfaction, quality of life and adherence. *Clin Med Res* 2008;6**:**54–67.

41. **Wei W,** Pan C, Xie L, Baser O. Association of treatment persistence and adherence with real-world outcomes among insulin-treated patients with type 2 diabetes mellitus (T2DM). *Diabetes* 2012; 61(1):A4.

42. **Gore M**, Brandenburg NA, Hoffman DL, *et al*. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006;**7**:892–900.

43. **Musich S**, Hook D, Baaner S, Edington DW. The association of two productivity measures with health risks and medical conditions in an Australian employee population. *Am J Health Promot* 2006;**20**:353–63.

44. **Sullivan PW**, Ghushchyan V, Wyatt HR, *et al*. Productivity costs associated with cardiometabolic risk factor clusters in the United States. *Value Health* 2007;**10**:443–50.

45. **Sullivan PW**, Ghushchyan V, Ben-Joseph RH. The effect of obesity and cardiometabolic risk factors on expenditures and productivity in the United States. *Obesity (Silver Spring)* 2008;**16**:2155–62.

46. **Kannan H**, Thompson S, Bolge SC. Economic and humanistic outcomes associated with comorbid type-2 diabetes, high cholesterol and hypertension among individuals who are overweight or obese. *J Occup Environ Med* 2008;**50**:542–9.

Figure legends

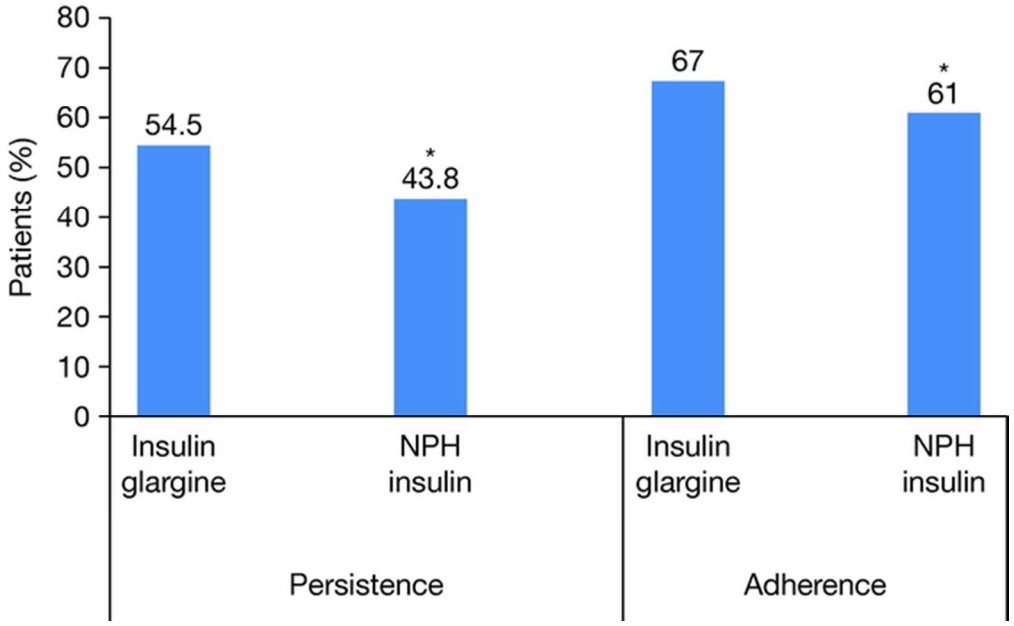
Figure 1 Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.

*P<0.05 vs insulin glargine

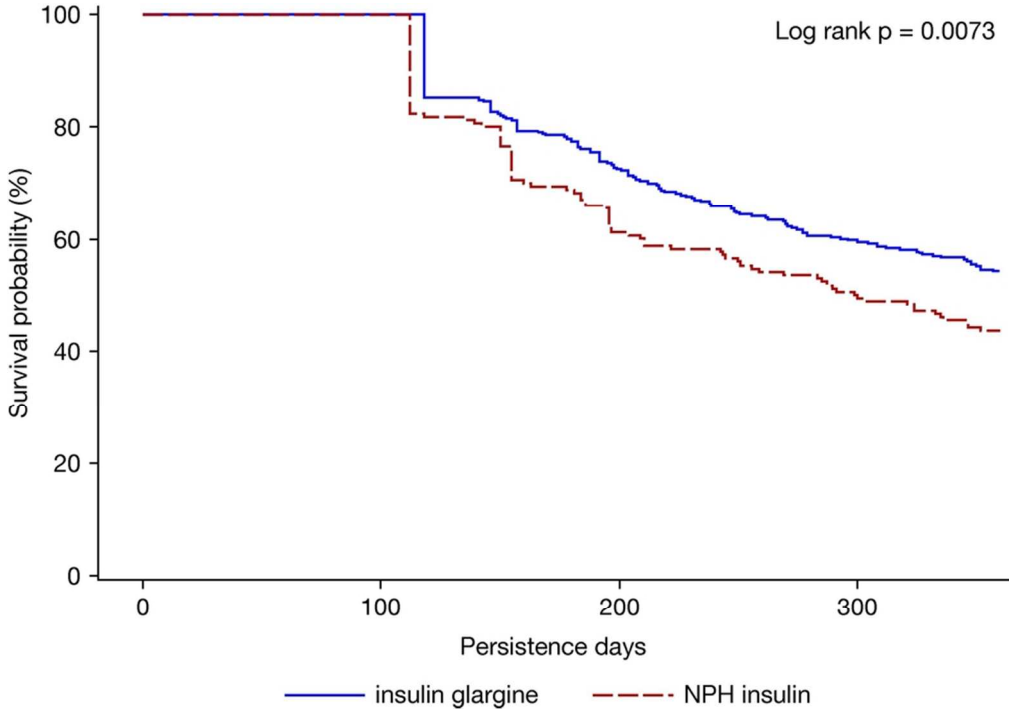
Figure 2 Kaplan–Meier Curve of follow-up 1 Year persistence days between insulin glargine and NPH insulin

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

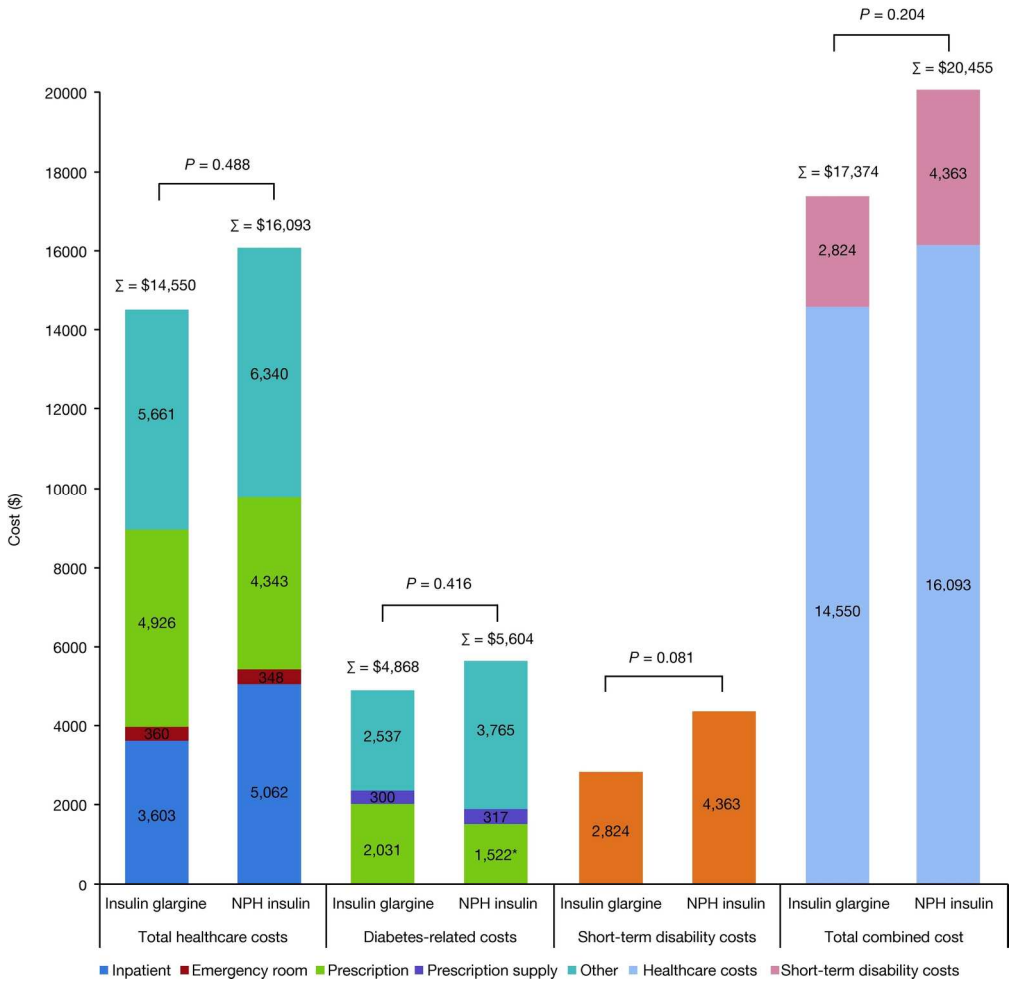
*P<0.0001 vs insulin glargine



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



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



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

	Study Section	Additional Remarks
Study Design		
(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	
Data Collection		
(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	
Analysis and Interpretation of Results		
(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	

	Study Section	Additional Remarks
(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

Corresponding author

Onur Baser

STATinMED Research

211 N. 4th Ave

Ann Arbor, MI 48104

Cell: (734) 646-7991

Work: (734) 222-5426

Fax:(734) 864-0359

Authors

Li Wang[1], Wenhui Wei[2], Raymond Miao[2], Lin Xie[1], Onur Baser[1,3]

1. STATinMED Research, Ann Arbor, MI, USA
2. sanofi-aventis US, Bridgewater, NJ, USA
3. The University of Michigan, Ann Arbor, MI, USA

Word count: 3,158

Article Summary

Aritcle 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 biasbetween 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-tem-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

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

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

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

who are adherent to medication.[23] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[21, 24]

Although there are data in support of the clinical benefits of basal insulins there is currently a paucity of real-world information about the impact of different basal insulin regimens on healthcare utilization, employee disability, and their associated costs from an employer's perspective.

METHODS

Database

This study is a retrospective analysis from the employer perspective, of patients' medical and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters Database 2003–2009. This database captures person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services from about 100 large employers, health plans, and government and public organizations.

Short-term disability data were extracted from the MarketScan Health and Productivity Management Database, which is an integrated database that contains information on absence, short-term disability, and workers' compensation experience. This information is linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial Claims and Encounters Database for these employees, providing a unique and valuable resource for examining health and productivity issues for an employed, privately insured population.

The MarketScan Research Databases are fully compliant with the letter and spirit of the Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board review was waived.

Cohort selection criteria

Included in the analysis were employees, but not their dependents, of 18 years of age or older with T2DM, defined as having made at least one inpatient visit or two physician visits dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine or NPH insulin with the date of the first such claim being the index date (prescriptions of

other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare benefits and work benefits for short-term disability for 3 months prior to insulin initiation (baseline period), and 12 months after insulin initiation (follow-up period); and on at least one oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The patient cohorts for comparison were determined on the basis of use of insulin glargine or NPH insulin at initiation of insulin therapy. Outcomes were compared between the matched cohorts after 1 year of follow-up.

Baseline characteristics

Data were analyzed to assess baseline characteristics, including: gender; age; OAD use; comorbidities; healthcare utilization/costs; and short-term disability for 3 months prior to insulin initiation for all patients. 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 previously published studies,[25-27] 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. For example, our analysis showed that for patients who filled prescription for 10 mL and refilled later, 90% of GLA patients refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered discontinuing GLA if he/she previously filled a prescription for 10mL of GLA but did not refill it within 119 days. 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 [28] (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) to correct the issue that almost all prescriptions are dispensed with a 30-day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in

the analysis period divided by the number of days in the analysis period) by the average number of days between insulin study drug prescription refills for patients using the insulin divided by the average days' supply for patients using the insulin. By using data based on the actual gap between the days' supply and the days to next refill, this adjustment is necessary to measure real adherent to the instructions from their doctors.

Clinical outcomes

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).[29] Daily average consumption (DACON) of insulin was estimated based on pharmacy claim data and calculated as the total number of units dispensed before the last refill of study drug divided by the total number of days between initiation and last refill during follow-up period. A1C data were not available in this study.

Healthcare resource utilization and cost

Categories of healthcare resource utilization included numbers of outpatient visits, emergency room (ER) visits, and inpatient admissions, inpatient length of stay (days), total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare 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),[30] which amounts to $168, since disability programs typically pay for 70% of lost income.[31]

Total cost

Total cost was assessed by combining direct costs (healthcare) 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 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 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 the 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. Before the matching, GLA patients were more likely to be male, older, using insulin pen, and had higher copayment than NPH patients (data not shown here), indicating confounding by indication as selection bias. The 2:1 PSM yielded a total of 534 patients (GLA: 356; NPH 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
Insulin Pen use, n (%)	59 (16.5%)	33 (18.5%)	
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 (%)			
Obesity	5 (1.4)	4 (2.2)	0.4758
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
Congestive heart failure	12 (3.3)	4 (2.2)	0.4728
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
Total healthcare utilization, n (%) or mean ± SD [median]			
Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]	0.3018
ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	25 (14.0%)	0.2550
Hospitalization/patient	0.16 ± 0.39 [0]	0.17 ± 0.42 [0]	0.6458
ER visits/patient	0.31 ± 0.67 [0]	0.28 ± 0.68 [0]	0.6817
Endocrinologist visits/patient	0.15 ± 0.48 [0]	0.19 ± 0.55 [0]	0.3844
Diabetes-related healthcare utilization, n (%) or mean ± SD [median]			
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]	0.11 ± 0.34 [0]	0.5570
Endocrinologist visits/patient	0.14 ± 0.47 [0]	0.17 ± 0.53 [0]	0.4951
Office visits/patient	1.74 ± 1.43 [1]	1.60 ± 1.44 [1]	0.2782
Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]	0.4975
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]	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

		Insulin glargine (n=356)	NPH insulin (n=178)	P value
Total diabetes-related healthcare cost, mean ± SD [median]	Total cost	5259 ± 14237 [1632]	4794 ± 10731 [1895]	0.6735
	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 (%)				0.8694
	$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 ± 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
Hypoglycemia, n (%) or mean ± SD			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
Total healthcare utilization, n (%) or mean ± SD			
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
Diabetes-related healthcare utilization, n (%) or mean ± SD			
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
Loss in productivity, mean ± SD			
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

costs for the insulin glargine cohort ($2,031), compared with the NPH insulin cohort ($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 0.36 per patient per year in the insulin glargine group, compared with 0.38 in the NPH insulin group (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 3). Combined total costs were similar between the insulins ($17,374 for GLA vs $20,455 for NPH, P=0.204).

Correlations

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 and 3:1 PSM yielded similar results overall. 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 $2,173vs $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 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations and endocrinologist visits were also numerically lower in GLA group but not statistically significant, probably due to sample size and the inaccuracy of using ICD-9-CM diagnosis code (250.xx) to capture diabetes-related events. In regard to short-term disability in both primary and sensitivity analyses, numerically fewer short-term disability days and lower associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort, but this was not significant. It is likely that the reduction in short-term disability is related to fewer hospitalizations in the insulin glargine cohort. Indeed, the correlation analysis showed that patients with any hospitalizations were significantly more likely to claim for short-term disability: both the number and duration of hospitalizations were highly correlated with the number of claims and the duration of short-term disability.

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

Basal insulin analogs have been shown to have several advantages compared to NPH insulin including less pharmacologic variability, lower risk of hypoglycemia, and greater impact on quality of life.[14-16, 40] The rates of hypoglycemia-related events were, however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated with less hypoglycemia than NPH insulin,[15] the switch from NPH insulin to insulin glargine may usually be considered in patients with evidence of hypoglycemia or increasing incidence

of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort in the present analysis may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.

The increased persistence associated with insulin glargine, as shown in this study, may lead to better clinical outcomes,[41] and potentially improve work-related outcomes.[13, 20, 23] Diabetes-related disability has been shown to result in loss of work place productivity.[42-46] In this study, we observed fewer short-term disability days in patients on insulin glargine, compared with those on NPH insulin. Although the differences were not statistically significant, this finding may suggest that initiation of therapy with insulin glargine could help increase workplace productivity among employed patients with T2DM compared with those initiating with NPH insulin.

As with all retrospective studies, issues of sampling bias should be taken into account when interpreting these results, which may introduce selection bias. The use of PSM methodology in this study should have helped reduce the impact of selection bias such as confounding by indication. In fact, three different matching ratios were tested, and all yielded similar findings. However, it likely limited patients in the insulin glargine cohort to those most similar to the NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further, some insulin patients may have been missed due to the availability of 90 day/mail order prescriptions resulting in them being missed during the 3 month baseline period.

This study has several limitations. Although the MarketScan data represent a large diverse population, it only included information from mainly large, self-insured employers, whose employees were more likely to locate in certain geographic areas than the general employee population, and the analysis included an convenience sample of patients whose employer supplied productivity data. Therefore, this study should not be assumed as representative of the overall US population. As any retrospective observational study, causality of treatment effects cannot be established in this study. Although the propensity score matching method was used to reduce the treatment selection bias issues such as confounding by indications, it also led to significant reduction in the sample size, particularly on the GLA group, due to the required matching ratios, and relatively much smaller sample size in NPH group. This may also makes the study underpowered to detect all significant differences between treatment groups. In addition, the similar rate of hypoglycemia observed between groups is inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia with insulin glargine, compared with NPH insulin.[9, 33] It is unlikely that rates of hypoglycemia would be captured with the same level of sensitivity in this retrospective

analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia rate in both cohorts may have resulted in insufficient statistical power to detect significant differences. Coding issues in the claim data may also have contributed to the lack of statistical robustness. The daily units of insulin (DACON) was measured based on pharmacy claim data and may not be accurate. For example, patients on a low dose are instructed to discard unused insulin (particularly in vials) after approximately 1 month, pharmacy claim data can lead to an overestimation of DACON. However, this is unlikely to affect GLA and NPH groups disproportionally because they were similar in proportion of patients using insulin pen. (Table 2) A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia could be assessed. Finally, the 12 month follow-up period of this study may not have been sufficient to detect benefits due to improved persistence and adherence.

CONCLUSION

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

ACKNOWLEDGEMENTS

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

DISCLOSURES

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

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

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 Baser obaser@statinmed.com

References

1. **US Centers for Disease Control and Prevention**. National diabetes fact sheet 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed 18 June 2012.
2. **Morsanutto A**, Berto P, Lopatriello S, *et al.* Major complications have an impact on total annual medical cost of diabetes: results of a database analysis. *J Diabetes Complications* 2006;**20**:163–9.
3. **Kim S**. Burden of Hospitalizations primarily due to incontrolled diabetes: implications of inadequate primary healthcare in the United States. *Diabetes Care* 2007;**30**:1281–2.
4. **Durden ED**, Alemayehu B, Bouchard JR*, et al*. Direct health care costs of patients with type 2 diabetes within a privately insured employed population, 2000 and 2005. *J Occup Environ Med* 2009;**51**:1460–5.
5. **American Diabetes Association**. *Diabetes Care* 2008;**31**:596–615.
6. **Gillum LA**, Gouveia C, Dorsey ER, *et al.* NIH disease funding levels and burden of disease. *PLoS One*. 2011;**6**:e16837.
7. **Rosenstock J**, M. Davies, Home PD, *et al.* A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;**51**:408–16.
8. **Mattila TK**, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010;**70**:2229–45.
9. **Rosenstock J**, Dailey G, Massi-Benedetti M, *et al.* Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;**28**:950–5.

10. **Mullins P**, Sharplin P, Yki-Järvinen H, *et al*. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;**29**:1607–19.
11. **Home PD**, Fritsche A, Schinzel S, Massi-Benedetti M. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;**12**:772–9.
12. **Riddle MC**. Making the transition from oral to insulin therapy. *Am J Med* 2005;**118(**suppl 5A):14S–20S.
13. Twenty-Four Hour Action of Insulin Glargine (Lantus) May Be too Short for Once-Daily Dosing: A case report
14. **Asche C**, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;**33**:74–109.
15. **Esposito K**, Chiodini P, Caouano A, *et al.* Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes. *Diabetes Care* 2012;**35**:2698–2705,
16. **Inzucchi SE**, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type2 diabetes: a patient-centered approach. *Diabetes Care* 2012;**35**:1364-79.
17. **Esposito K,** Capuano A, Giugliano D. Humalog (lispro) for type 2 diabetes. *Expert Opin Biol Ther* 2012;**12**:1541-50.
18. **Cooke CE**, Lee HY, Tong YP, Haines ST. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr Med Res Opin* 2010;**26**:231–8.
19. **Jansà M,** Hernández C, Vidal M, et al. Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. *Patient Educ Couns* 2010;**81**:161–8.

20. **Gibson TB,** Song X, Alemayehu B, Wang SS, Waddell JL, Bouchard JR, Forma F. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care* 2010;**16**:589–600.
21. **Sokol MC**, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–30.
22. **Stuart B**, Davidoff A, Lopert R, *et al*. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health Serv Res* 2011;**46**:1180–99.
23. **Sprince NL**, Pospisil S, Peek-Asa C. Occupational injuries among workers with diabetes: the National Health Interview Survey, 1997–2005. J Occup Environ Med 2008;**50**:804–8.
24. **Rizzo JA**, Abbott TA, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. *Health Econ* 1996;**5**:249–65.
25. **Davis SN,** Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract* 2011;**17**:845–52.
26. **Xie L,** Wei W, Pan C, et al. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. *Adv Ther* 2011;28: 1000-11.
27. **Xie L,** Zhou S, Wei W et al. Does Pen Help? A Real-World Outcomes Study of Switching from Vial to Disposable Pen Among Insulin Glargine-Treated Patients with Type 2 Diabetes Mellitus. Diabetes Technol Ther 2013 Jan 21. [Epub ahead of print]
28. **Baser O**, Bouchard J, DeLuzio T, *et al*. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;**27**:94–104.
29. **Zhao Y**, Campbell CR, Fonseca V, Shi L Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* 2012;**35**:1126–32.
30. **Goetzel RZ**, Long SR, Ozminkowski RJ, *et al*. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.

31. **Hawkins K**, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *J Occup Environ Med* 2007;**49**:368–74.
32. **Rosenbaum PR,** Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
33. **Rhoads GG**, Dain MP, Zhang Q, Kennedy L. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. *Diabetes Obes Metab* 2011;**13**:711–7.
34. **Clissold R**, Clissold S. Insulin glargine in the management of diabetes mellitus: an evidence-based assessment of its clinical efficacy and economic value. *Core Evid* 2007**;2**:89–110.
35. **Grima DT**, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics* 2007;**25**:253–66.
36. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. *Int J Clin Pharmacol Ther* 2007;**45**:203–20.
37. **Schöffski O**, Breitscheidel L, Benter U, *et al*. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;**11**:695–712.
38. **Lee LJ**, Yu AP, Johnson SJ, *et al*. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pract* 2010;**87**:108–16.
39. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther* 2011;**49**:217–30.

40. **Hartman I.** Insulin analogs: impact on treatment success, satisfaction, quality of life and adherence. *Clin Med Res* 2008;6**:**54–67.

41. **Wei W,** Pan C, Xie L, Baser O. Association of treatment persistence and adherence with real-world outcomes among insulin-treated patients with type 2 diabetes mellitus (T2DM). *Diabetes* 2012; 61(1):A4.

42. **Gore M**, Brandenburg NA, Hoffman DL, *et al*. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006;**7**:892–900.

43. **Musich S**, Hook D, Baaner S, Edington DW. The association of two productivity measures with health risks and medical conditions in an Australian employee population. *Am J Health Promot* 2006;**20**:353–63.

44. **Sullivan PW**, Ghushchyan V, Wyatt HR, *et al*. Productivity costs associated with cardiometabolic risk factor clusters in the United States. *Value Health* 2007;**10**:443–50.

45. **Sullivan PW**, Ghushchyan V, Ben-Joseph RH. The effect of obesity and cardiometabolic risk factors on expenditures and productivity in the United States. *Obesity (Silver Spring)* 2008;**16**:2155–62.

46. **Kannan H**, Thompson S, Bolge SC. Economic and humanistic outcomes associated with comorbid type-2 diabetes, high cholesterol and hypertension among individuals who are overweight or obese. *J Occup Environ Med* 2008;**50**:542–9.

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 persistence days between insulin glargine and NPH insulin

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

*P<0.0001 vs insulin glargine

BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002348.R2
Article Type:	Research
Date Submitted by the Author:	01-Apr-2013
Complete List of Authors:	Wang, Li; STATinMED Research, Wei, Wenhui; sanofi-aventis US, Miao, Raymond; sanofi-aventis US, Xie, Lin; STATinMED Research, Baser, Onur; STATinMED Research, ; The University of Michigan,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics, Pharmacology and therapeutics
Keywords:	healthcare utilization, employee productivity, diabetes costs

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

Corresponding author

Onur Baser

STATinMED Research

211 N. 4th Ave

Ann Arbor, MI 48104

Cell: (734) 646-7991

Work: (734) 222-5426

Fax:(734) 864-0359

Authors

Li Wang[1], Wenhui Wei[2], Raymond Miao[2], Lin Xie[1], Onur Baser[1,3]

1. STATinMED Research, Ann Arbor, MI, USA
2. sanofi-aventis US, Bridgewater, NJ, USA
3. The University of Michigan, Ann Arbor, MI, USA

Word count: 3,338

Article Summary

Aritcle 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 restrospective 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-tem-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.

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

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

insulin.[23] 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.[24]

Although there are data in support of the clinical benefits of basal insulins, there is currently a paucity of real-world information about the impact of different basal insulin regimens on healthcare utilization, employee disability, and their associated costs from an employer's perspective. This analysis was performed in order to compare real-world outcomes from initiating insulin glargine or NPH insulin among employees with T2DM who had both employer-sponsored health insurance and short-tem-disability coverages. As insulin detemir, another long-acting basal insulin analog, was only launched in the US in 2006, too few patients were being treated with this agent for it to be included in the analysis as a comparator.

METHODS

Database

This study is a retrospective analysis from the employer perspective of patients' medical and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters Database 2003–2009. This database captures person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services from about 100 large employers, health plans, and government and public organizations.

Short-term disability data were extracted from the MarketScan Health and Productivity Management Database, which is an integrated database that contains information on absence, short-term disability, and workers' compensation experience. This information is linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial Claims and Encounters Database for these employees, providing a unique and valuable resource for examining health and productivity issues for an employed, privately insured population.

The MarketScan Research Databases are fully compliant with the letter and spirit of the Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board review was waived.

Cohort selection criteria

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

Baseline characteristics

Data were analyzed to assess baseline characteristics, including: gender, age, OAD use, comorbidities, healthcare utilization/costs, index drug co-pay, and short-term disability for 3 months prior to insulin initiation for all patients. 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 previously published studies,[25-27] persistence was measured here as the time the patient had remained on study drug 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. For example, our analysis showed that for patients who filled a prescription for 10 mL and refilled later, 90% of insulin glargine patients refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered to have discontinued insulin glargine if he/she previously filled a prescription for 10mL of insulin glargine but did not refill it within 119 days. 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 [28] (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) to correct the issue that almost all prescriptions are dispensed with a 30-day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in the analysis period divided by the number of days in the analysis period) by the average number of days between insulin study drug prescription refills for patients using the insulin divided by the average days' supply for patients using the insulin. By using data based on the actual gap between the days' supply and the days to next refill, this adjustment is necessary to measure real adherence to doctor's instructions.

Clinical outcomes

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).[29] Daily average consumption (DACON) of insulin was estimated based on pharmacy claims data and calculated as the total number of units dispensed before the last refill of study drug divided by the total number of days between initiation and last refill during follow-up period. Glycated hemoglobin (A1C) data were not available in this study.

Healthcare resource utilization and cost

Categories of healthcare resource utilization included numbers of outpatient visits, emergency room (ER) visits, inpatient admissions, inpatient length of stay (days), and total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare 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),[30] which amounts to $168, since disability programs typically pay for 70% of lost income.[31]

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 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 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. Kaplan–Meier survival curves and the log-rank test were used to compare 1-year treatment persistence. Relationships between treatment persistence and hospitalization as well as short-term disability were investigated by the chi-squared test. 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 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 ± SD	49 ± 10	49 ± 10	0.7580
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
Pen use for Initiated Insulin, n (%)	59 (16.5%)	33 (18.5%)	0.5706
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 (%)			
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
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
Healthcare utilization, n (%) or mean ± SD [median]			
All-cause Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
All-cause Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]	0.3018
All-cause ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	25 (14.0%)	0.2550
Diabetes-related Hospitalizations	34 (9.5%)	20 (11.2%)	0.5426
Diabetes-related Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]	0.4975
Diabetes-related ER visits	37 (10.3%)	17 (9.5%)	0.7608
Any hypoglycemia visit, n (%)	15 (4.2%)	6 (3.4%)	0.9197
Total healthcare cost, mean ± 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
Hypoglycemia, n (%) or mean ± SD			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
Healthcare utilization, n (%) or mean ± SD			
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
Loss in productivity, mean ± SD			
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

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.

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).

DISCUSSION

In this real-world study, use of insulin glargine was associated with better persistence and adherence than NPH insulin. In addition, 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 fewer hospitalizations, fewer total endocrinologist visits, and lower inpatient costs associated with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalizations and endocrinologist visits were also numerically lower in the group using insulin glargine but not statistically significant, probably due to sample size and the inaccuracy of using ICD-9-CM diagnosis code (250.xx) to capture diabetes-related events. In regard to short-term disability in both primary and sensitivity analyses, numerically fewer short-term disability days and lower associated costs were reported in the insulin glargine cohort than in the NPH insulin cohort, but this was not significant. It is likely that the reduction in short-term disability is related to better persistence with treatment in the insulin glargine cohort. Indeed, the correlation analysis showed that treatment persistence and short-term disability were highly correlated.

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

Basal insulin analogs have been shown to have several advantages compared to NPH insulin, including less pharmacologic variability, lower risk of hypoglycemia, and greater impact on quality of life.[18, 20, 21, 40] The rates of hypoglycemia-related events were, however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated with less hypoglycemia than NPH insulin,[20] the switch from NPH insulin to insulin glargine may usually be considered in patients with evidence of hypoglycemia or increasing incidence of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort in the present analysis may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.

The increased persistence associated with insulin glargine, as shown in this study, may lead to better clinical outcomes,[41] and potentially improve work-related outcomes.[9, 12, 19] Diabetes-related disability has been shown to result in loss of work-place productivity.[42-46] In this study, we observed fewer short-term disability days in patients on insulin glargine, compared with those on NPH insulin. Although the differences were not statistically significant, this finding may suggest that initiation of therapy with insulin glargine could help increase workplace productivity among employed patients with T2DM compared with those initiating with NPH insulin.

As with all retrospective studies, issues of sampling bias should be taken into account when interpreting these results, which may introduce selection bias. The use of PSM methodology in this study should have helped reduce the impact of selection bias. In fact, three different matching ratios were tested, and all yielded similar findings. However, PSM likely limited patients in the insulin glargine cohort to those most similar to the NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further, some insulin patients may have been missed due to the availability of 90-day/mail order prescriptions resulting in their being missed during the 3-month baseline period.

This study has several limitations. Although the MarketScan data represent a large diverse population, the study only included information from mainly large, self-insured employers, whose employees were more likely to be located in certain geographic areas than the general employee population, and the analysis included a convenience sample of patients whose employer supplied productivity data. Therefore, this study should not be assumed to be representative of the overall US population. As with any retrospective observational study, causality of treatment effects cannot be established in this study. Although the PSM method was used to balance differences between the two groups included in the study,

confounding by indication or prognosis may still have affected the outcomes observed. The use of PSM also led to a significant reduction in the sample size, particularly in the insulin glargine group, due to the required matching ratios, and a much smaller sample size in the NPH group. This may also make the study underpowered to detect all significant differences between treatment groups. In addition, the similar rate of hypoglycemia observed between groups is inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia with insulin glargine, compared with NPH insulin.[15, 33] It is unlikely that rates of hypoglycemia would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia rate in both cohorts may have resulted in insufficient statistical power to detect significant differences. Coding issues in the claim data may also have contributed to the lack of statistical robustness. The DACON was measured based on pharmacy claim data and may not be accurate. For example, patients on a low dose are instructed to discard unused insulin (particularly in vials) after approximately 1 month; hence, pharmacy claim data can lead to an overestimation of DACON. However, this is unlikely to affect the study groups disproportionally because they were similar in proportion of patients using insulin pens (table 2). A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia could be assessed. Finally, the 12-month follow-up period of this study may not have been sufficient to detect benefits due to improved persistence and adherence.

CONCLUSION

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

ACKNOWLEDGEMENTS

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

DISCLOSURES

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

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

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

References

1. **US Centers for Disease Control and Prevention**. National diabetes fact sheet 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed 18 June 2012.
2. **Morsanutto A**, Berto P, Lopatriello S, *et al.* Major complications have an impact on total annual medical cost of diabetes: results of a database analysis. *J Diabetes Complications* 2006;**20**:163–9.
3. **Kim S**. Burden of hospitalizations primarily due to uncontrolled diabetes: implications of inadequate primary healthcare in the United States. *Diabetes Care* 2007;**30**:1281–2.
4. **Durden ED**, Alemayehu B, Bouchard JR*, et al*. Direct health care costs of patients with type 2 diabetes within a privately insured employed population, 2000 and 2005. *J Occup Environ Med* 2009;**51**:1460–5.
5. **American Diabetes Association**. *Diabetes Care* 2008;**31**:596–615.
6. **Gillum LA**, Gouveia C, Dorsey ER, *et al.* NIH disease funding levels and burden of disease. *PLoS One*. 2011;**6**:e16837.
7. **Mattila TK**, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010;**70**:2229–45.
8. **Asche C**, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;**33**:74–109.
9. **Gibson TB,** Song X, Alemayehu B, *et al*. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care* 2010;**16**:589–600.
10. **Sokol MC**, McGuigan KA, Verbrugge RR, *et al*. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–30.
11. **Stuart B**, Davidoff A, Lopert R, *et al*. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health Serv Res* 2011;**46**:1180–99.
12. **Sprince NL**, Pospisil S, Peek-Asa C *et al*. Occupational injuries among workers with diabetes: the National Health Interview Survey, 1997–2005. J Occup Environ Med 2008;**50**:804–8.

13. **Rizzo JA**, Abbott TA 3rd, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. *Health Econ* 1996;**5**:249–65.
14. **Rosenstock J**, M. Davies, Home PD, *et al.* A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;**51**:408–16.
15. **Rosenstock J**, Dailey G, Massi-Benedetti M, *et al*. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;**28**:950–5.
16. **Mullins P**, Sharplin P, Yki-Järvinen H, *et al*. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;**29**:1607–19.
17. **Home PD**, Fritsche A, Schinzel S, *et al*. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;**12**:772–9.
18. **Riddle MC**. Making the transition from oral to insulin therapy. *Am J Med* 2005;**118(**suppl 5A):14S–20S.
19. **Clement S**, Bowen-Wright H. Twenty-four hour action of insulin glargine (Lantus) may be too short for once-daily dosing: a case report. *Diabetes Care* 2002;**25**:1479–80.
20. **Esposito K**, Chiodini P, Capuano A, *et al.* Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes. *Diabetes Care* 2012;**35**:2698–2705.
21. **Inzucchi SE**, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type2 diabetes: a patient-centered approach. *Diabetes Care* 2012;**35**:1364–79.
22. **Esposito K,** Capuano A, Giugliano D. Humalog (lispro) for type 2 diabetes. *Expert Opin Biol Ther* 2012;**12**:1541–50.

23. **Cooke CE**, Lee HY, Tong YP, *et al*. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr Med Res Opin* 2010;**26**:231–8.
24. **Jansà M,** Hernández C, Vidal M, *et al.* Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. *Patient Educ Couns* 2010;**81**:161–8.
25. **Davis SN,** Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract* 2011;**17**:845–52.
26. **Xie L,** Wei W, Pan C, *et al*. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. *Adv Ther* 2011;28: 1000-11.
27. **Xie L,** Zhou S, Wei W, *et al*. Does pen help? A real-world outcomes study of switching from vial to disposable pen among insulinglargine-treated patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 2013;**15**:230–6.
28. **Baser O**, Bouchard J, DeLuzio T, *et al*. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;**27**:94–104.
29. **Zhao Y**, Campbell CR, Fonseca V, *et al*. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* 2012;**35**:1126–32.
30. **Goetzel RZ**, Long SR, Ozminkowski RJ, *et al*. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.
31. **Hawkins K**, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *J Occup Environ Med* 2007;**49**:368–74.
32. **Rosenbaum PR**, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.

33. **Rhoads GG**, Dain MP, Zhang Q, *et al*. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. *Diabetes Obes Metab* 2011;**13**:711–7.
34. **Clissold R**, Clissold S. Insulin glargine in the management of diabetes mellitus: an evidence-based assessment of its clinical efficacy and economic value. *Core Evid* 2007;**2**:89–110.
35. **Grima DT**, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics* 2007;**25**:253–66.
36. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. *Int J Clin Pharmacol Ther* 2007;**45**:203–20.
37. **Schöffski O**, Breitscheidel L, Benter U, *et al*. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;**11**:695–712.
38. **Lee LJ**, Yu AP, Johnson SJ, *et al*. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pract* 2010;**87**:108–16.
39. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther* 2011;**49**:217–30.
40. **Hartman I**. Insulin analogs: impact on treatment success, satisfaction, quality of life and adherence. *Clin Med Res* 2008;6:54–67.

41. **Wei W**, Pan C, Xie L, *et al*. Association of treatment persistence and adherence with real-world outcomes among insulin-treated patients with type 2 diabetes mellitus (T2DM). *Diabetes.* 2012;**61**:A4.
42. **Gore M**, Brandenburg NA, Hoffman DL, *et al*. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006;**7**:892–900.
43. **Musich S**, Hook D, Baaner S, *et al*. The association of two productivity measures with health risks and medical conditions in an Australian employee population. *Am J Health Promot* 2006;**20**:353–63.
44. **Sullivan PW**, Ghushchyan V, Wyatt HR, *et al*. Productivity costs associated with cardiometabolic risk factor clusters in the United States. *Value Health* 2007;**10**:443–50.
45. **Sullivan PW**, Ghushchyan V, Ben-Joseph RH. The effect of obesity and cardiometabolic risk factors on expenditures and productivity in the United States. *Obesity (Silver Spring)* 2008;**16**:2155–62.
46. **Kannan H**, Thompson S, Bolge SC. Economic and humanistic outcomes associated with comorbid type-2 diabetes, high cholesterol and hypertension among individuals who are overweight or obese. *J Occup Environ Med* 2008;**50**:542–9.

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

Figure 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

Additional File 1

EVEREST Statement: Checklist for health economics paper

	Study Section	Additional Remarks
Study Design		
(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	
Data Collection		
(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	
Analysis and Interpretation of Results		
(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	

	Study Section	Additional Remarks
(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

Corresponding author

Onur Baser

STATinMED Research

211 N. 4th Ave

Ann Arbor, MI 48104

Cell: (734) 646-7991

Work: (734) 222-5426

Fax:(734) 864-0359

Authors

Li Wang[1], Wenhui Wei[2], Raymond Miao[2], Lin Xie[1], Onur Baser[1,3]

1. STATinMED Research, Ann Arbor, MI, USA
2. sanofi-aventis US, Bridgewater, NJ, USA
3. The University of Michigan, Ann Arbor, MI, USA

Word count: 3,3315~~5~~8

Article Summary

Aritcle 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 s~~sources of bias in this restrospective 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~~ 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-tem-disability coverages~~-~~.

Design: Retrospective cohort study

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

Participants: Adult employees wi~~+~~th 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~~S~~election 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

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 analysis yielded similar findings.

Conclusion:

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

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.[~~8~~7] Adherence to anti-hyperglycemic ~~medication~~interventions is also associated with improved glycemic control and decreased healthcare resource utilization[~~14~~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.[~~20~~9] Moreover, although adherence is associated with higher drug costs, overall healthcare costs decrease in adherent patients with diabetes and other chronic conditions.[~~24~~10, ~~22~~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.[~~23~~12] Effective pharmacological management of diabetes with adequate compliance also results in substantial cost benefits to employers.[~~24~~10, ~~24~~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.[~~7~~14] ~~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.[~~9~~15-~~11~~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.[~~12~~18] ~~Although~~However, twice-daily use of insulin glargine might be required to achieve therapeutic goals in some patients with T2DM.[~~13~~19] ~~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~~20-~~17~~22]. In reality, patients taking insulin glargine have been shown to be more likely to persist with their medication than those taking NPH insulin.[~~18~~23] 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~~24]

Although there are data in support of the clinical benefits of basal insulins, there is currently a paucity of real-world information about the impact of different basal insulin regimens on healthcare utilization, employee disability, and their associated costs from an employer's perspective. This analysis was performed in order to ~~provide~~ compare real-world outcomes from initiating insulin glargine or NPH insulin among employees with T2DM who had both employer-sponsored health insurance and short-tem-disability coverages. As insulin detemir, another long-acting basal insulin analog, was only launched in the US in 2006, too few patients were being treated with this agent for it to be included in the analysis as a comparator.

METHODS

Database

This study is a retrospective analysis from the employer perspective~~,~~ of patients' medical and pharmacy claims extracted from the MarketScan Commercial Claims and Encounters Database 2003–2009. This database captures person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services from about 100 large employers, health plans, and government and public organizations.

Short-term disability data were extracted from the MarketScan Health and Productivity Management Database, which is an integrated database that contains information on absence, short-term disability, and workers' compensation experience. This information is linkable to the medical, pharmacy, and enrolment data in the MarketScan Commercial Claims and Encounters Database for these employees, providing a unique and valuable resource for examining health and productivity issues for an employed, privately insured population.

The MarketScan Research Databases are fully compliant with the letter and spirit of the Health Insurance Portability and Accountability Act of 1996 and Institutional Review Board review was waived.

Cohort selection criteria

Included in the analysis were employees, but not their dependents, of 18 years of age or older with T2DM, defined as having made at least one inpatient visit or two physician visits dated at least 30 days apart, with a primary or secondary diagnosis of diabetes mellitus type II or unspecified type not stated as uncontrolled (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 250.x0) or diabetes mellitus type II or unspecified type uncontrolled (code 250.x2); at least one pharmacy claim of insulin glargine or NPH insulin with the date of the first such claim being the index date (prescriptions of other basal insulins too low for inclusion); enrolled for medical and pharmacy healthcare benefits and work benefits for short-term disability for 3 months prior to insulin initiation (baseline period)~~,~~ and 12 months after insulin initiation (follow-up period); and on at least one oral antidiabetic drug (OAD) or exenatide, but no insulin, during the baseline period. The patient cohorts for comparison were determined on the basis of use of insulin glargine or NPH insulin at initiation of insulin therapy. Patients initiating insulin detemir were excluded from the current study because it was only available after 200~~5~~76, and thus an insufficient number of patients (fewer than 100) was identified in the database to provide adequate statistical power for meaningful comparisons. Outcomes were compared between the matched cohorts after 1 year of follow-up.

Baseline characteristics

Data were analyzed to assess baseline characteristics, including: gender~~;~~, age~~;~~, OAD use~~;~~, comorbidities~~;~~, healthcare utilization/costs~~;~~, index drug co-pay, and short-term disability for 3 months prior to insulin initiation for all patients. 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 previously published studies,[25-27] persistence was measured here as the time the patient had remained on study drug~~s~~ 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. For example, our analysis showed that for patients who filled a prescription for 10 mL and refilled later, 90% of ~~GLA~~ insulin glargine patients refilled it within 119 days versus 113 days for NPH patients. Subsequently, a patient was considered ~~discontinuing~~ to have discontinued ~~GLA~~ insulin glargine if he/she previously filled a prescription for 10mL of ~~GLA~~ insulin glargine but did not refill it within 119 days. 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 [28] (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) to correct the issue that almost all prescriptions are dispensed with a 30-day supply documented by the pharmacy. The adjusted MPR was calculated by multiplying the traditional MPR (the total days' supply of all filled insulin glargine or NPH prescriptions in the analysis period divided by the number of days in the analysis period) by the average number of days between insulin study drug prescription refills for patients using the insulin divided by the average days' supply for patients using the insulin. By using data based on the actual gap between the days' supply and the days to next refill, this adjustment is necessary to measure real adherence to doctor's instructions.

Clinical outcomes

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).[29] Daily average consumption (DACON) of insulin was estimated based on pharmacy claims data and calculated as the total number of units dispensed before the last refill of study drug divided by the total number of days between initiation and last refill during follow-up period. Glycated hemoglobin (A1C) data were not available in this study.

Healthcare resource utilization and cost

Categories of healthcare resource utilization included numbers of outpatient visits, emergency room (ER) visits, ~~and~~ inpatient admissions, inpatient length of stay (days), and total outpatient pharmacy claims (average outpatient claims). Diabetes-specific healthcare

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),[30] which amounts to $168, since disability programs typically pay for 70% of lost income.[31]

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~~s, 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
~~Insulin~~ Pen use for Initiated Insulin, 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 (%)				

	Insulin glargine (n=356)	NPH insulin (n=178)	P value
~~Obesity~~	~~5 (1.4)~~	~~4 (2.2)~~	~~0.4758~~
Hypertension	76 (21.3)	39 (21.9)	0.8817
Hyperlipidemia	39 (10.9)	22 (12.3)	0.6305
~~Congestive heart failure~~	~~12 (3.3)~~	~~4 (2.2)~~	~~0.4728~~
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
~~Total H~~healthcare utilization, n (%) or mean ± SD [median]			
All-cause Hospitalizations	53 (14.8%)	28 (15.7%)	0.7980
All-cause Total hospitalization days	0.97 ± 3.38 [0]	0.72 ± 2.11 [0]	0.3018
All-cause ER visits	80 (22.4%)	38 (21.3%)	0.7680
Endocrinologist visits	38 (10.6%)	25 (14.0%)	0.2550
~~Hospitalization/patient~~	~~0.16 ± 0.39 [0]~~	~~0.17 ± 0.42 [0]~~	~~0.6458~~
~~ER visits/patient~~	~~0.31 ± 0.67 [0]~~	~~0.28 ± 0.68 [0]~~	~~0.6817~~
~~Endocrinologist visits/patient~~	~~0.15 ± 0.48 [0]~~	~~0.19 ± 0.55 [0]~~	~~0.3844~~
~~Diabetes-related healthcare utilization, n (%) or mean ± SD [median]~~			
Diabetes-related Hospitalizations	34 (9.5%)	20 (11.2%)	0.5426
Diabetes-related Total hospitalization days	0.52 ± 2.31 [0]	0.41 ± 1.49 [0]	0.4975
Diabetes-related 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]~~	~~0.11 ± 0.34 [0]~~	~~0.5570~~
~~Endocrinologist visits/patient~~	~~0.14 ± 0.47 [0]~~	~~0.17 ± 0.53 [0]~~	~~0.4951~~
~~Office visits/patient~~	~~1.74 ± 1.43 [1]~~	~~1.60 ± 1.44 [1]~~	~~0.2782~~
~~Total hospitalization days~~	~~0.52 ± 2.31 [0]~~	~~0.41 ± 1.49 [0]~~	~~0.4975~~
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]	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
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%)	
~~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~~)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 ~~2~~1). 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
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
Hypoglycemia, n (%) or mean ± SD			
Patients with hypoglycemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycemia claims/patient	0.10 ± 0.63	0.07 ± 0.44	0.5902
~~Total~~ Hhealthcare utilization, n (%) or mean ± SD			
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
~~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~~
~~**Diabetes-related healthcare utilization, n (%) or mean ± SD**~~			
Diabetes-related Hospitalizations	45 (12.6%)	27 (15.1%)	0.4201
Diabetes-related 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~~
Loss in productivity, mean ± SD			

Formatted: Font: Not Bold

Formatted: Font: Not Bold

	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 26.9%; 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 2)~~ ~~($1,522) (P<0.001).~~

Loss in productivity and its associated costs

~~In terms of loss in productivity and the associated costs for employers,~~ T~~t~~he 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 ~~3~~2). 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 $2,173vs $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

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

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

Basal insulin analogs have been shown to have several advantages compared to NPH insulin, including less pharmacologic variability, lower risk of hypoglycemia, and greater impact on quality of life.[1~~4-16~~8, 20, 21, 40] The rates of hypoglycemia-related events were, however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated with less hypoglycemia than NPH insulin,[~~15~~20] the switch from NPH insulin to insulin glargine may usually be considered in patients with evidence of hypoglycemia or increasing incidence of hypoglycemic events. The baseline hypoglycemic event results between cohorts in this study were similar, and thus it is possible that the NPH insulin cohort in the present analysis may be skewed to patients with lower NPH insulin-related hypoglycemia than expected.

The increased persistence associated with insulin glargine, as shown in this study, may lead to better clinical outcomes,[41] and potentially improve work-related outcomes.[~~13~~9, 12, 19~~,~~ ~~20, 23~~] Diabetes-related disability has been shown to result in loss of work~~-~~-place productivity.[42-46] In this study, we observed fewer short-term disability days in patients on insulin glargine, compared with those on NPH insulin. Although the differences were not

statistically significant, this finding may suggest that initiation of therapy with insulin glargine could help increase workplace productivity among employed patients with T2DM compared with those initiating with NPH insulin.

As with all retrospective studies, issues of sampling bias should be taken into account when interpreting these results, which may introduce selection bias. The use of PSM methodology in this study should have helped reduce the impact of selection bias ~~such as confounding by indication~~. In fact, three different matching ratios were tested, and all yielded similar findings. However, ~~it~~ PSM likely limited patients in the insulin glargine cohort to those most similar to the NPH insulin cohort and not to those patients with T2DM who use insulin in general. Further, some insulin patients may have been missed due to the availability of 90-day/mail order prescriptions resulting in ~~them~~ their being missed during the 3-month baseline period.

This study has several limitations. Although the MarketScan data represent a large diverse population, ~~it~~ the study only included information from mainly large, self-insured employers, whose employees were more likely to be located in certain geographic areas than the general employee population, and the analysis included a~~n~~ convenience sample of patients whose employer supplied productivity data. Therefore, this study should not be assumed ~~as~~ to be representative of the overall US population. As with any retrospective observational study, causality of treatment effects cannot be established in this study. Although the PSM method was used to balance differences between the two groups included in the study, confounding by indication or prognosis may still have affected the outcomes observed. The use of PSM ~~to reduce the treatment selection bias issues such as confounding by indications, it~~ also led to a significant reduction in the sample size, particularly ~~on~~ in the ~~GLA~~ insulin glargine group, due to the required matching ratios, and ~~relatively~~ a much smaller sample size in the NPH group. This may also make~~s~~ the study underpowered to detect all significant differences between treatment groups. In addition, the similar rate of hypoglycemia observed between groups is inconsistent with existing literature, as previous studies suggest a lower risk of hypoglycemia with insulin glargine, compared with NPH insulin.[~~9~~15, 33] It is unlikely that rates of hypoglycemia would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomized clinical trial. Moreover, the low overall hypoglycemia rate in both cohorts may have resulted in insufficient statistical power to detect significant differences. Coding issues in the claim data may also have contributed to the lack of statistical robustness. The ~~daily units of insulin (~~DACON~~)~~ was measured based on pharmacy claim data and may not be accurate. For example, patients on a low dose are instructed to discard unused insulin (particularly in vials) after approximately 1 month~~,~~; hence, pharmacy claim data can lead to an overestimation of

DACON. However, this is unlikely to affect ~~GLA and NPH~~the study groups disproportionally because they were similar in proportion of patients using insulin pens (~~Table~~ table 2). A1C data were not available, so neither the effectiveness of glycemic control nor the association with hypoglycemia could be assessed. Finally, the 12-~~-~~month follow-up period of this study may not have been sufficient to detect benefits due to improved persistence and adherence.

CONCLUSION

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

ACKNOWLEDGEMENTS

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

DISCLOSURES

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

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

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~~ are available by e-mailing Dr Onur Baser obaser@statinmed.com

References

1. **US Centers for Disease Control and Prevention**. National diabetes fact sheet 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed 18 June 2012.
2. **Morsanutto A**, Berto P, Lopatriello S, *et al*. Major complications have an impact on total annual medical cost of diabetes: results of a database analysis. *J Diabetes Complications* 2006;**20**:163–9.
3. **Kim S**. Burden of hospitalizations primarily due to uncontrolled diabetes: implications of inadequate primary healthcare in the United States. *Diabetes Care* 2007;**30**:1281–2.
4. **Durden ED**, Alemayehu B, Bouchard JR, *et al*. Direct health care costs of patients with type 2 diabetes within a privately insured employed population, 2000 and 2005. *J Occup Environ Med* 2009;**51**:1460–5.
5. **American Diabetes Association**. *Diabetes Care* 2008;**31**:596–615.
6. **Gillum LA**, Gouveia C, Dorsey ER, *et al*. NIH disease funding levels and burden of disease. *PLoS One*. 2011;**6**:e16837.
7. **Mattila TK**, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010;**70**:2229–45.
8. **Asche C**, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;**33**:74–109.
9. **Gibson TB,** Song X, Alemayehu B, *et al*. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care* 2010;**16**:589–600.
10. **Sokol MC**, McGuigan KA, Verbrugge RR, *et al*. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–30.
11. **Stuart B**, Davidoff A, Lopert R, *et al*. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health Serv Res* 2011;**46**:1180–99.
12. **Sprince NL**, Pospisil S, Peek-Asa C *et al*. Occupational injuries among workers with diabetes: the National Health Interview Survey, 1997–2005. J Occup Environ Med 2008;**50**:804–8.

13. **Rizzo JA**, Abbott TA 3rd, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. *Health Econ* 1996;**5**:249–65.
14. **Rosenstock J**, M. Davies, Home PD, *et al*. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;**51**:408–16.
15. **Rosenstock J**, Dailey G, Massi-Benedetti M, *et al*. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;**28**:950–5.
16. **Mullins P**, Sharplin P, Yki-Järvinen H, *et al*. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;**29**:1607–19.
17. **Home PD**, Fritsche A, Schinzel S, *et al*. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab* 2010;**12**:772–9.
18. **Riddle MC**. Making the transition from oral to insulin therapy. *Am J Med* 2005;**118(**suppl 5A):14S–20S.
19. **Clement S**, Bowen-Wright H. Twenty-four hour action of insulin glargine (Lantus) may be too short for once-daily dosing: a case report. *Diabetes Care* 2002;**25**:1479–80.
20. **Esposito K**, Chiodini P, Capuano A, *et al*. Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes. *Diabetes Care* 2012;**35**:2698–2705.
21. **Inzucchi SE**, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type2 diabetes: a patient-centered approach. *Diabetes Care* 2012;**35**:1364–79.
22. **Esposito K,** Capuano A, Giugliano D. Humalog (lispro) for type 2 diabetes. *Expert Opin Biol Ther* 2012;**12**:1541–50.

23. **Cooke CE**, Lee HY, Tong YP, *et al*. Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization. *Curr Med Res Opin* 2010;**26**:231–8.

24. **Jansà M,** Hernández C, Vidal M, *et al*. Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. *Patient Educ Couns* 2010;**81**:161–8.

25. **Davis SN,** Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract* 2011;**17**:845–52.

26. **Xie L,** Wei W, Pan C, *et al*. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. *Adv Ther* 2011;28: 1000-11.

27. **Xie L,** Zhou S, Wei W, *et al*. Does pen help? A real-world outcomes study of switching from vial to disposable pen among insulinglargine-treated patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 2013;**15**:230–6.

28. **Baser O**, Bouchard J, DeLuzio T, *et al*. Assessment of adherence and healthcare costs of insulin device (FlexPen) versus conventional vial/syringe. *Adv Ther* 2010;**27**:94–104.

29. **Zhao Y**, Campbell CR, Fonseca V, *et al*. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* 2012;**35**:1126–32.

30. **Goetzel RZ**, Long SR, Ozminkowski RJ, *et al*. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers. *J Occup Environ Med* 2004;**46**:398–412.

31. **Hawkins K**, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *J Occup Environ Med* 2007;**49**:368–74.

32. **Rosenbaum PR**, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.

33. **Rhoads GG**, Dain MP, Zhang Q, *et al*. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. *Diabetes Obes Metab* 2011;**13**:711–7.

34. **Clissold R**, Clissold S. Insulin glargine in the management of diabetes mellitus: an evidence-based assessment of its clinical efficacy and economic value. *Core Evid* 2007;**2**:89–110.

35. **Grima DT**, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics* 2007;**25**:253–66.

36. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. *Int J Clin Pharmacol Ther* 2007;**45**:203–20.

37. **Schöffski O**, Breitscheidel L, Benter U, *et al*. Resource utilisation and costs in patients with type 2 diabetes mellitus treated with insulin glargine or conventional basal insulin under real-world conditions in Germany: LIVE-SPP study. *J Med Econ* 2008;**11**:695–712.

38. **Lee LJ**, Yu AP, Johnson SJ, *et al*. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pract* 2010;**87**:108–16.

39. **Brändle M**, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther* 2011;**49**:217–30.

40. **Hartman I**. Insulin analogs: impact on treatment success, satisfaction, quality of life and adherence. *Clin Med Res* 2008;6:54–67.

41. **Wei W**, Pan C, Xie L, *et al*. Association of treatment persistence and adherence with real-world outcomes among insulin-treated patients with type 2 diabetes mellitus (T2DM). *Diabetes*. 2012;**61**:A4.

42. **Gore M**, Brandenburg NA, Hoffman DL, *et al*. Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006;**7**:892–900.

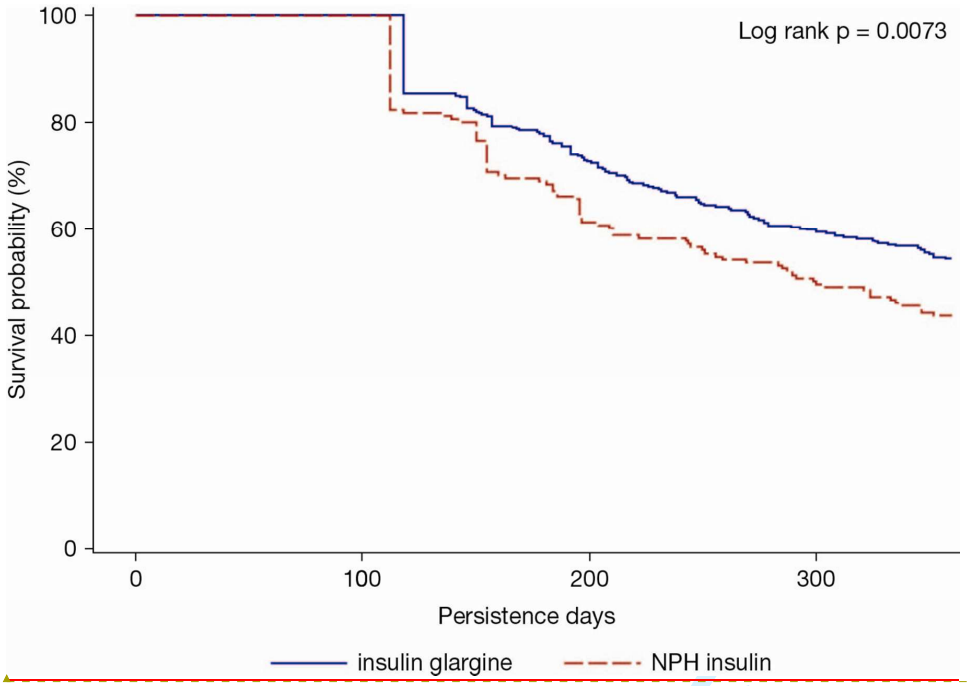
43. **Musich S**, Hook D, Baaner S, *et al*. The association of two productivity measures with health risks and medical conditions in an Australian employee population. *Am J Health Promot* 2006;**20**:353–63.

44. **Sullivan PW**, Ghushchyan V, Wyatt HR, *et al*. Productivity costs associated with cardiometabolic risk factor clusters in the United States. *Value Health* 2007;**10**:443–50.

45. **Sullivan PW**, Ghushchyan V, Ben-Joseph RH. The effect of obesity and cardiometabolic risk factors on expenditures and productivity in the United States. *Obesity (Silver Spring)* 2008;**16**:2155–62.

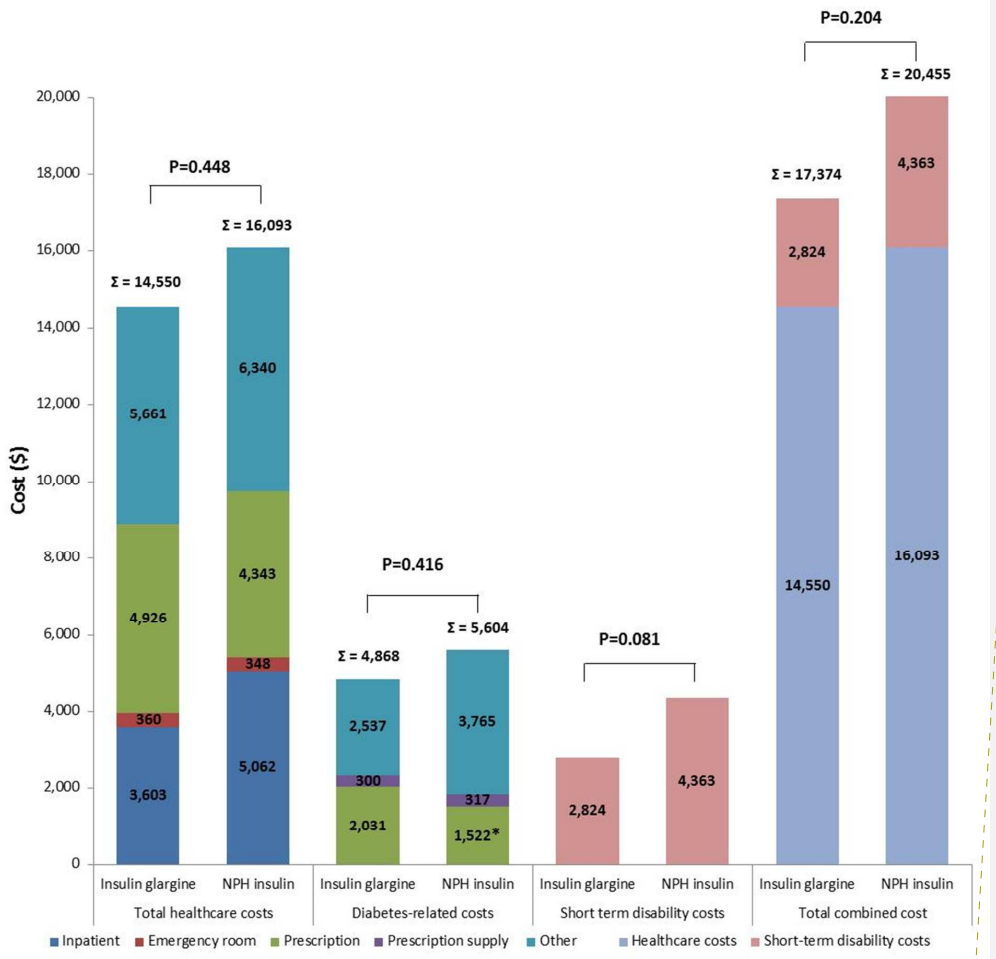
46. **Kannan H**, Thompson S, Bolge SC. Economic and humanistic outcomes associated with comorbid type-2 diabetes, high cholesterol and hypertension among individuals who are overweight or obese. *J Occup Environ Med* 2008;**50**:542–9.

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



Formatted: Font: 12 pt

Figure 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

Formatted: Font: Bold, Font color: Custom Color(RGB(0,0,204))

~~**Figure legends**~~

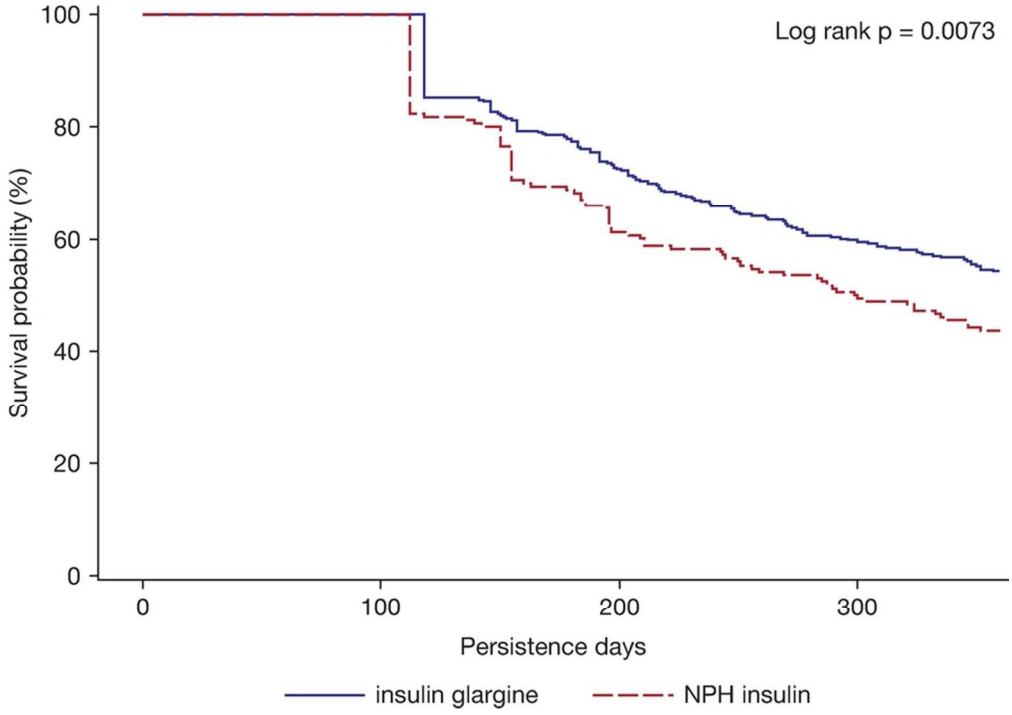
~~**Figure 1** Persistence (90th percentile) and adherence with insulin therapy: 1-year follow-up.~~

~~*P<0.05 vs insulin glargine~~

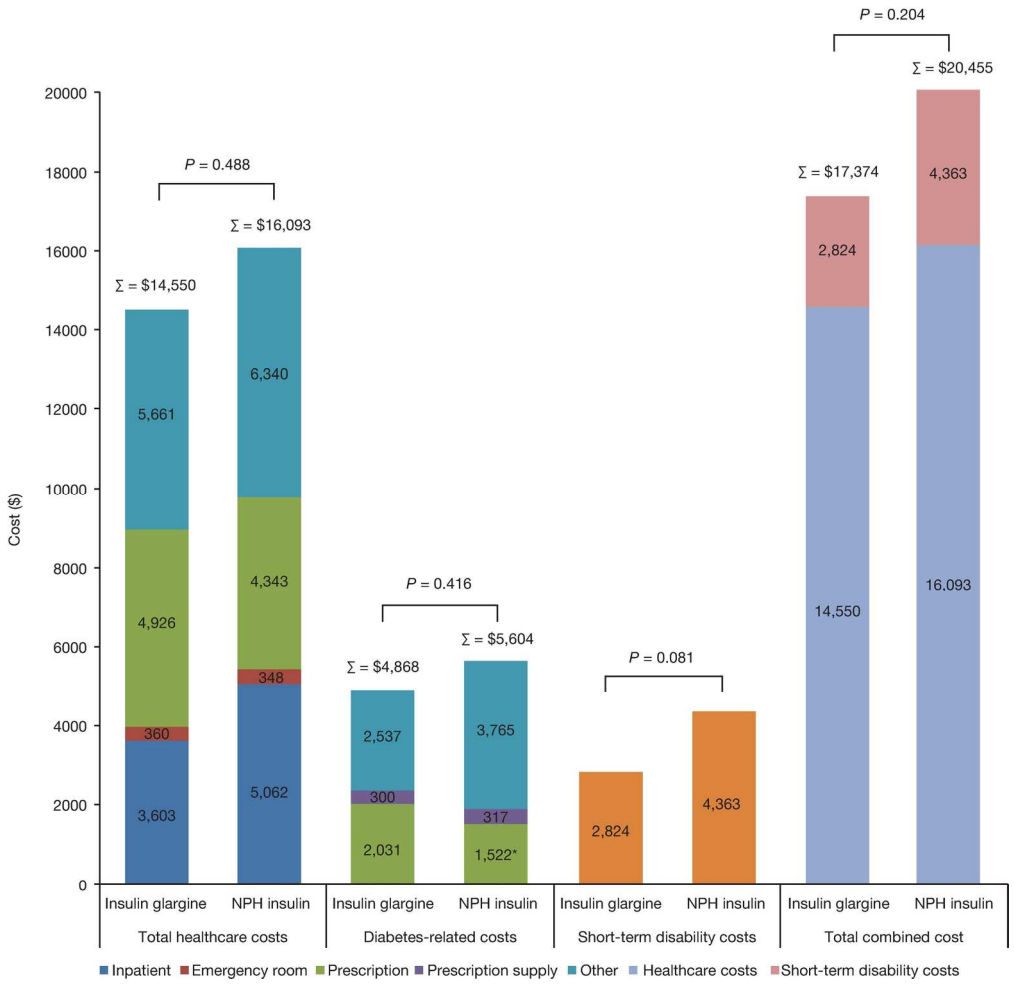
~~**Figure 2** 1 Kaplan–Meier Curve of follow-up 1 Year year persistence days between insulin glargine and NPH insulin~~

~~**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~~



81x57mm (300 x 300 DPI)



181x175mm (300 x 300 DPI)