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

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ABSTRACT

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

Design: Retrospective cohort study.

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

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

Primary and secondary outcome measures:

Outcomes during 1-year follow-up were measured and compared: insulin treatment persistence and adherence; hypoglycaemia rates and daily average consumption of insulin; total and diabetes-specific healthcare resource utilisation 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 analysed (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 hospitalisation (23% vs 31.4%; $p = 0.036$) and endocrinologist visits (19.1% vs 26.9%; $p = 0.038$), similar hypoglycaemia rates (both 4.4%; $p = 1.0$), higher diabetes drug costs (\$2031 vs \$1522; $p < 0.001$), but similar total healthcare costs (\$14 550 vs \$16 093; $p = 0.448$) and total diabetes-related healthcare costs (\$4686 vs \$5604; $p = 0.416$). Short-term disability days and costs were numerically lower in the GLA cohort (16.0 vs 24.5 days; $p = 0.086$ and \$2824 vs \$4363; $p = 0.081$, respectively). Sensitivity analyses yielded similar findings.

ARTICLE SUMMARY

Article focus

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

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.

Conclusions: Insulin GLA 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 USA, 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

ARTICLE SUMMARY

Strengths and limitations of this study

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

USA,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 antihyperglycaemic interventions is also associated with improved glycaemic control and decreased healthcare resource utilisation⁸ 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 minimised 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 analogues provides clinically relevant improvements in glycaemic control with a good safety profile.¹⁴ Options for basal insulin include insulin glargine, a long-acting basal insulin analogue, 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 hypoglycaemia, particularly nocturnal hypoglycaemia, 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 outcome 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 utilisation, 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-term-disability coverages. As insulin detemir, another long-acting basal insulin analogue, was only launched in the USA 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 utilisation, expenditures and enrolment across inpatient, outpatient, prescription drug and carve-out services from about 100 large employers, health plans and government and public organisations.

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 the Institutional Review Board review was waived.

Cohort selection criteria

Included in the analysis were employees, but not their dependants, aged 18 years 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 T2DM 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 were 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 available only after 2006, and thus an insufficient number of patients (fewer than 100) were 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 analysed to assess baseline characteristics, including: gender, age, OAD use, comorbidities, healthcare utilisation/costs, index drug copay and short-term disability for 3 months prior to insulin initiation for all patients. Follow-up records were analysed to assess treatment persistence, adherence, hypoglycaemic events, healthcare resource utilisation, 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 the study drug without discontinuation or switching following insulin initiation. Study medication was considered to be 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 vs 113 days for NPH patients. Subsequently, a patient was considered to have discontinued insulin glargine if he/she previously filled a prescription for 10 ml 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 the insulin-device package size²⁸ (insulin glargine, eg, is packaged either in 10 ml vials with a total of 1000 units or in a 3 ml disposable device in a package of 5 pens with a total of 1500 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 the doctor's instructions.

Clinical outcomes

Hypoglycaemia was defined as a healthcare encounter (outpatient, inpatient or emergency department visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycaemia (ICD-9 code 250.8—diabetes with other specified manifestations; 251.0—hypoglycaemic coma; 251.1—other specified hypoglycaemia or 251.2—hypoglycaemia, 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 the study drug divided by the total number of days between initiation and last refill during the follow-up period. Glycated haemoglobin (HbA1c) data were not available in this study.

Healthcare resource utilisation and cost

Categories of healthcare resource utilisation included the number 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 utilisation included claims with a primary diagnosis of diabetes (ICD-9-CM: 250.xx) and the use of antihyperglycaemic 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 programmes 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) methodology³² 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 hypothesised confounding relationship with the outcome variables, and included age, gender, region, health plan type, Charlson Comorbidity Index and baseline concomitant medications, hypoglycaemic events, healthcare utilisation (overall or disease-related), copays 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 analysed 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. The Kaplan-Meier survival curves and the log-rank test were used to compare 1-year treatment persistence. Relationships between treatment persistence and hospitalisation as well as short-term disability were investigated by the χ^2 test. *p* Values of <0.05 were taken to be indicative of a significant difference.

RESULTS

Baseline characteristics

Data from 2454 patient records were eligible for the 1-year follow-up analyses: 2250 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 the insulin pen and having a higher copayment than those using NPH (data not shown). 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).

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*=0.0073; figure 1). Sensitivity analyses using the 75th and 95th percentiles yielded similar results (75th percentile: 34% 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).

Clinical outcomes

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

Healthcare utilisation and cost

During follow-up, patients in the insulin glargine cohort had lower rates of hospitalisation and of endocrinologist visits, compared with those in the NPH insulin cohort (table 2). All diabetes-related healthcare utilisation 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 the 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 vs 24.5 days, *p*=0.086 and \$2824 vs \$4363, *p*=0.081, respectively; figure 2). The 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 hospitalisation (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).

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
Hyperlipidaemia	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 utilisation, n (%) or mean±SD (median)			
All-cause hospitalisations	53 (14.8)	28 (15.7)	0.7980
All-cause total hospitalisation 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 hospitalisations	34 (9.5%)	20 (11.2%)	0.5426
Diabetes-related total hospitalisation 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 hypoglycaemia 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
Diabetes supply cost	48±97 (0)	46±92 (0)	0.7766
Total cost	1934±6551 (621)	1450±3485 (596)	0.2658
Copay 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%)	

Continued

Table 1 Continued

	Insulin glargine (n=356)	NPH insulin (n=178)	p Value
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 the index date.

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

DISCUSSION

In this real-world study, the use of insulin glargine was associated with better persistence and adherence than NPH insulin. In addition, lower healthcare resource utilisation was associated with insulin glargine than NPH insulin, in terms of hospitalisations and endocrinologist visits, over 1 year of follow-up. Rates of hypoglycaemia-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 the 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 hospitalisations, fewer total endocrinologist visits and lower inpatient costs associated with the use of insulin glargine, compared with NPH insulin. Diabetes-related hospitalisations and endocrinologist visits were also numerically lower in the group using

insulin glargine but not statistically significant, probably due to the sample size and the inaccuracy of using the ICD-9-CM diagnosis code (250.xx) to capture diabetes-related events. In regard to the 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 the 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 glycaemic control as NPH

Table 2 Follow-up treatment persistence, hypoglycaemia, healthcare utilisation 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
Hypoglycaemia, n (%) or mean±SD			
Patients with hypoglycaemia	16 (4.4)	8 (4.4)	1.0000
Hypoglycaemia claims/patient	0.10±0.63	0.07±0.44	0.5902
Healthcare utilisation, n (%) or mean±SD			
Hospitalisations	82 (23%)	56 (31.4%)	0.0360
Total hospitalisation days	1.29±4.54 (0)	2.06±4.98 (0)	0.0754
# Hospitalisations/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 Hospitalisations	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.

Figure 1 Kaplan-Meier curve of follow-up 1 year persistence days between insulin glargine and neutral protamine Hagedorn insulin.

insulin, and to be cost effective in a range of countries and settings.^{33–39}

Basal insulin analogues have been shown to have several advantages compared with NPH insulin, including less pharmacological variability, a lower risk of hypoglycaemia and a greater impact on quality of life.^{18 20 21 40} The rates of hypoglycaemia-related events were, however, similar for insulin glargine and NPH insulin in this study. Since insulin glargine is associated with less hypoglycaemia than NPH insulin,²⁰ the switch from NPH insulin to insulin glargine may usually be considered in patients with evidence of hypoglycaemia or an increasing incidence of hypoglycaemic events. The baseline hypoglycaemic 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 hypoglycaemia 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 workplace 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, these findings 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 very 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 hypoglycaemia observed between groups is inconsistent with that in the existing literature, as previous studies suggest a lower risk of hypoglycaemia with insulin glargine, compared with NPH insulin.^{15 33} It is unlikely that rates of hypoglycaemia would be captured with the same level of sensitivity in this retrospective analysis as they would in a randomised clinical trial. Moreover, the low overall hypoglycaemia rate in both

Figure 2 One-year short-term disability and direct healthcare costs. (Total between-group differences did not reach statistical significance.) * $p < 0.0001$ versus insulin glargine.

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. 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 disproportionately because they had a similar proportion of patients using insulin pens (table 2). HbA1c data were not available, and therefore neither the effectiveness of glycaemic control nor the association with hypoglycaemia 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 healthcare utilisation, 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. Owing to the retrospective nature of this study, further studies need to be conducted to confirm these findings.

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