Real-world rates, predictors, and associated costs of hypoglycemia among patients with type 2 diabetes mellitus treated with insulin glargine: results of a pooled analysis of six retrospective observational studies

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Original article

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Abstract

Objective:
To evaluate the real-world rates of hypoglycemia and related costs among patients with type 2 diabetes mellitus (T2DM) who initiated insulin glargine with either a disposable pen or vial-and-syringe.

Methods:
Pooled data were evaluated from six previously published, retrospective, observational studies using US health plan insurance claims databases to investigate adults with T2DM who initiated insulin glargine. The current study evaluated baseline characteristics, hypoglycemic events, and costs during the 6 months prior to and 12 months following insulin glargine initiation. Comparisons were made between patients initiating treatment with a disposable pen (GLA-P) and vial-and-syringe (GLA-V). Multivariate analyses using baseline characteristics as covariates determined predictors of hypoglycemia after initiating insulin glargine.

Results:
This study included 23,098 patients (GLA-P: 14,911; GLA-V: 8187). Overall annual prevalence of hypoglycemia was low (6.3% overall, 2.2% related to hospital admission or emergency department visit). Prevalence was significantly lower with GLA-P (5.5% vs 7.7%; $p < 0.0001$). Furthermore, average glycated hemoglobin HbA1c reduction was higher with GLA-P (-1.22% vs -0.86%; $p = 0.0012$). The average annual hypoglycemia-related cost associated with initiating insulin glargine was \$293, with GLA-P being 46% lower than GLA-V (\$225 vs \$417; $p = 0.001$). Patients who had already developed microvascular complications at the time of initiating insulin therapy were at higher risk for developing hypoglycemia.

Limitations:
This study is limited by the use of retrospective data and ICD-9-CM codes, which are subject to coding error. In addition, this pooled analysis used unmatched cohorts, with multivariate regression analyses employed to adjust for between-group differences. Finally, results describe a managed care sample and cannot be generalized to all patients with T2DM.

Conclusions:
Patients with T2DM initiating insulin glargine treatment showed low rates of hypoglycemia, especially when using a disposable pen device. Hypoglycemia-related costs were low, contributing a very small proportion to overall diabetes-related healthcare costs.

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by a progressive loss of beta-cell function and insulin hyposecretion; in order to achieve adequate glycemic control, most patients with T2DM will eventually require insulin[1]. Despite the well-known benefits of early insulin initiation[2], many patients face protracted and unnecessary delays in initiating insulin therapy[3] due to treatment barriers among patients and providers alike[1,4,5]. Hypoglycemia is a common complication of insulin therapy and a leading limiting factor of anti-diabetes therapy[6]. Furthermore, in patients with T2DM, hypoglycemia has a substantial negative impact on the patient's quality-of-life in terms of physical, mental, and social functioning[7]. Short-term effects of hypoglycemia relate to the symptoms associated with the actual hypoglycemic episode and risks of dangerous situations[7,8]. On the long-term, hypoglycemia has been shown to have a major impact on work productivity, weight gain, and increased risk for cardiovascular complications, but also behavioral changes, including loss of self-confidence, anxiety, and fear of future episodes[7,8].

In addition, hypoglycemia is associated with a higher risk of anti-diabetes treatment discontinuation and a significantly increased financial burden for the patient, the healthcare system, and the society[7,9–12].

Cost-driving factors induced by hypoglycemia include hospital admissions, emergency visits, out-of-pocket expenses required to manage hypoglycemic events, but also the indirect costs associated with the reduced quality-of-life, reduced work capacity, and increased long-term complications[8,10].

The selection of treatments to provide good glycemic control with the lowest possible risk of hypoglycemia is an important consideration for healthcare decision-makers looking to provide the best possible, cost-effective treatment strategy care for patients with T2DM[7]. Glycemic control and hypoglycemic complications may be influenced by the type of insulin and the delivery method used. Insulin glargine is a long-acting basal insulin analog that, compared with conventional insulin therapy, has a significantly reduced hypoglycemia occurrence that may result in cost savings[13]. Although direct medication costs are higher with insulin pens compared with vial-and-syringe systems, using insulin pens improves patient adherence and may reduce the occurrence of hypoglycemia without increasing total healthcare costs[5,14].

Clinical studies using glucose-confirmed hypoglycemia can provide information about the association between anti-diabetes treatments and the risk of hypoglycemia. Real-world studies using claims-based data on hypoglycemia provide particularly valuable information about the impact of hypoglycemia on healthcare costs; these hypoglycemic events may represent more severe events requiring assistance and medical care. This claims-based study was designed to evaluate the real-world rates of hypoglycemia and related healthcare costs among patients with T2DM who initiated insulin glargine with either a disposable pen or vial-and-syringe. It represents the perspective of US payers with regard to hypoglycemia-related costs incurred, and as such is not designed to capture wider societal costs associated with diabetes.

Patients and methods

This pooled analysis evaluated patient-level data collected from US health plan administrative claims databases. Data from six previously published, retrospective, observational studies of T2DM patients initiating insulin glargine were included[14–19]. Each included study compared initiation of insulin glargine administered using a disposable pen (SoloSTAR®, sanofi-aventis U.S., Bridgewater, NJ) with other injectable therapy (insulin glargine vial-and-syringe (Lantus®, sanofi-aventis U.S.), insulin detemir disposable pen (FlexPen®, Novo Nordisk A/S, Bagsværd, Denmark), or the incretin mimetic, exenatide (Byetta®, Amylin Pharmaceuticals, Inc., San Diego, CA)). Although stringent 1:1 propensity score matching[20] was used in each study to ensure that treatment cohorts were comparable in observed baseline characteristics, the analysis used pooled patient-level data from two unmatched cohorts of patients and only included data from the insulin glargine disposable pen (GLA-P) and vial-and-syringe (GLA-V) cohorts. Individual patients were not identifiable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Patient selection criteria

Potential study candidates were patients with T2DM, defined as having at least one inpatient visit or two physician visits dated at least 30 days apart with a primary or secondary diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 250.x0 or 250.x2. In addition, patients were required to be at least 18 years old at the time of insulin glargine initiation (index date) and to have previously received treatment with oral anti-diabetes drugs (OADs) or glucagon-like peptide-1 receptor agonists prior to initiating GLA-P or GLA-V between January 2007 and December 2009. Patients were required to have continuous health plan coverage for at least 6 months prior to (baseline or pre-index period) and for at least 1 year after (follow-up period) initiating insulin glargine. Duplicate patient records were removed when pooling the data.

Outcome measures

Baseline patient characteristics were recorded. Outcome measures included hypoglycemia at follow-up and hypoglycemia claim-related costs. The identification of hypoglycemic events was based on ICD-9-CM codes, consistent with the codes published by Zhao et al.[21]. Hypoglycemia was defined as a healthcare encounter (outpatient, inpatient, or emergency department [ED] visit) with a primary or secondary ICD-9-CM diagnosis code for hypoglycemia (ICD-9-CM code 250.8–diabetes with other specified manifestations; 251.0–hypoglycemic coma; 251.1–other specified hypoglycemia; or 251.2–hypoglycemia, unspecified)[22]. A limitation of retrospective observational claims data studies is the unavailability of glucose-confirmed hypoglycemia data. Therefore, in order to capture information on severity of hypoglycemia, the setting of hypoglycemia diagnosis was used as a proxy of severity; severe and non-severe hypoglycemia were defined as inpatient/ ED hypoglycemia and outpatient hypoglycemia, respectively. Follow-up hypoglycemic events during the 1-year follow-up period included all hypoglycemic events, including recorded inpatient, outpatient, and ED hypoglycemic events. Hypoglycemia claim-related costs included costs related to total hypoglycemia claims and inpatient, outpatient, and ED hypoglycemia claim-related costs.

The prevalence and event rates of hypoglycemia and associated healthcare costs were measured over the 1-year follow-up period and compared for GLA-P and GLA-V initiators. Prevalence was defined as the proportion of patients experiencing at least one hypoglycemic event during the 1-year follow-up. Event rate was defined as the number of hypoglycemic events per patient-year during the 1-year follow-up. Healthcare costs were computed as plan-paid amounts of adjudicated claims[17], total paid amount[14–16,19], and total charge[18]. In order to remove the cost bias that originates from different databases, the final cost variable for the pooled analysis was determined as the percentage of costs divided by total cost or diabetes-related total cost.

Statistical analysis

Descriptive statistics were used for demographics and other baseline variables to describe differences between the GLA-P and GLA-V cohorts. Baseline factors assessed included age at the time of insulin initiation, gender, glycated hemoglobin A1C (HbA1c) level, OAD use, comorbidities, total and diabetes-related healthcare utilization and costs, and hypoglycemia.

Correlation analyses were used to determine the relationship between the number of hypoglycemic events and HbA1c reduction from baseline. Multivariate analyses, using baseline characteristics as a covariate, were conducted to determine predictors of hypoglycemia during the 1-year follow-up. Logistic regression analysis was used to examine the relationship between baseline characteristics and the probability of experiencing any hypoglycemic event, or hypoglycemic events related to hospitalization or ED visit during the 1-year follow-up period. Negative binomial regression analyses were used to explore the relationship between baseline characteristics and the number of any hypoglycemic events or inpatient/ED hypoglycemic events during the 1-year follow-up period.

Results

Baseline characteristics

A total of 26,118 patients were included in the six retrospective observational studies, with 23,098 meeting criteria for the current study (GLA-P: $n = 14,911$; GLA-V: $n = 8187$). The mean age of all patients at index date was 54.1 years: 53.5% were men, the mean Charlson comorbidity index (CCI) score was 0.55 and patients were previously treated with a mean of 2.45 OADs. In the 2554 patients with available data (GLA-P: $n = 1,812$; GLA-V: $n = 742$), the mean baseline HbA1c value was 9.34%. Baseline data are summarized in Table 1.

Prevalence and hypoglycemia event rates during 1-year follow-up

During the 1-year follow-up, overall prevalence of any hypoglycemic event and inpatient/ED hypoglycemic events was low (6.27% and 2.19%, respectively) (Figure 1). The prevalence of hypoglycemia was significantly lower for GLA-P patients compared with GLA-V patients ($p < 0.0001$). Similarly, overall event rates of any hypoglycemia and inpatient/ED hypoglycemia were low (0.26 and 0.04 events/patient-year, respectively), and significantly lower for GLA-P compared with GLA-V patients ($p < 0.0001$; Figure 1).

Among those patients with available baseline and follow-up HbA1c data ($n = 2554$), the average HbA1c reduction from baseline was −1.22% in GLA-P patients compared with −0.86% in GLA-V patients ($p = 0.0012$). The number of hypoglycemic events was significantly correlated with reduction in HbA1c from baseline ($r = -0.152$; $p < 0.0001$).

The average HbA1c reduction was higher for patients who had inpatient/ED hypoglycemia during the follow-up compared with patients who only had outpatient hypoglycemia during the follow-up (−1.65% [median −1.4%] vs −1.57% [median −1.0%]). However, a higher frequency of inpatient/ED hypoglycemia was not significantly associated with a higher HbA1c reduction.

Table 1. Baseline demographics and clinical characteristics.

	GLA-P (n = 14,911)	GLA-V (n = 8187)	*p*-value for between-group comparison	All GLA-treated patients (n = 23,098)
Age at year of index date, years, mean (SD)	53.9 (9.3)	54.5 (9.8)	<0.0001	54.1 (9.5)
Female, n (%)	6993 (46.8)	3757 (45.8)	0.1416	10,750 (46.5)
HbA1c,* mean % (SD)	9.37 (1.96)	9.27 (2.09)	0.2583	9.34 (2.00)
Comorbidities				
CCI, mean (SD)	0.51 (1.18)	0.62 (1.30)	<0.0001	0.55 (1.23)
Hypertension, n (%)	7031 (47.1)	4277 (52.2)	<0.0001	11,308 (48.9)
Hyperlipidemia, n (%)	6859 (45.9)	3949 (48.2)	0.0011	10,808 (46.7)
Mental illness, n (%)	1503 (10.0)	1012 (12.3)	<0.0001	2515 (10.8)
Neuropathy, n (%)	1249 (8.3)	757 (9.2)	0.0247	2006 (8.6)
Retinopathy, n (%)	1009 (6.7)	642 (7.8)	0.0024	1651 (7.1)
Nephropathy, n (%)	564 (3.7)	334 (4.0)	0.2637	898 (3.8)
Anti-diabetes drugs				
Number of OADs, mean (SD)	2.48 (1.18)	2.39 (1.16)	<0.0001	2.45 (1.17)
Metformin, n (%)	12,073 (80.9)	6503 (79.4)	0.0049	18,576 (80.4)
Sulfonylureas, n (%)	10,034 (67.2)	5532 (67.5)	0.6664	15,566 (67.3)
Thiazolidinediones, n (%)	5945 (39.8)	3181 (38.8)	0.1310	9126 (39.5)
Sitagliptin, n (%)	3128 (20.9)	1424 (17.3)	<0.0001	4552 (19.7)
Exenatide, n (%)	2723 (18.2)	1204 (14.7)	<0.0001	3927 (17.0)
Healthcare utilization, n (%)				
Any hospitalization	2067 (13.8)	1556 (19.0)	<0.0001	3623 (15.6)
Any ED visit	1538 (10.3)	1101 (13.4)	<0.0001	2639 (11.4)
Any office visit	9515 (63.8)	7990 (97.5)	<0.0001	17,505 (75.7)
Any endocrinologist visit	2334 (15.6)	750 (9.1)	<0.0001	3084 (13.3)
Hypoglycemia, n (%)				
Any hypoglycemia	489 (3.2)	343 (4.1)	0.0004	832 (3.6)
Any inpatient/ED hypoglycemia	154 (1.9)	133 (1.6)	0.0001	287 (1.2)
# of Hypoglycemia, mean (SD)				
Any hypoglycemia	0.08 (0.98)	0.11 (0.98)	0.0416	0.09 (0.98)
Inpatient/ED hypoglycemia	0.01 (0.11)	0.02 (0.15)	<0.0001	0.02 (0.12)
Costs, $, mean (SD)				
Total costs	9612 (27,260)	12,168 (31,932)	<0.0001	10,518 (29,027)
Diabetes-related total costs	3812 (12,777)	4853 (15,136)	<0.0001	4181 (13,669)
Total hypoglycemia claim-related costs	152 (2621)	247 (4456)	0.0773	186 (3388)

*HbA1c data were available from 2554 patients (GLA-P, n = 1812; GLA-V, n = 742).
CCI, Charlson comorbidity index; ED, emergency department; GLA, insulin glargine; GLA-P, insulin glargine with disposable pen; GLA-V, insulin glargine with vial-and-syringe; OAD, oral anti-diabetic drug; SD, standard deviation.

Healthcare costs associated with hypoglycemia during 1-year follow-up

The average annual hypoglycemia-related cost associated with initiating insulin glargine was 46% lower for GLA-P compared with GLA-V patients ($225 vs $417; $p = 0.001$). The overall hypoglycemia-related cost contributed to 0.75% of the overall healthcare cost and 1.50% of the diabetes-related healthcare cost; again, a significant benefit ($p < 0.0001$) was observed for GLA-P compared with GLA-V patients (Figure 2).

When considering only inpatient/ED hypoglycemia-related costs, the average annual cost associated with initiating insulin glargine was $198, which amounted to 0.35% of the total cost and 0.59% of the total diabetes-related cost. As for the overall hypoglycemia-related cost, inpatient/ED hypoglycemia-related costs were significantly lower in the GLA-P cohort compared with the GLA-V cohort (Figure 2).

Compared with patients who only experienced out-patient hypoglycemia during the 1-year follow-up, patients with inpatient/ED hypoglycemia had higher overall and diabetes-related healthcare costs. This was mainly due to increased inpatients/ED costs. However, a higher frequency of inpatient/ED hypoglycemia did not correlate with higher healthcare costs.

Predictors of risk for hypoglycemia during 1-year follow-up

After adjusting for other confounding factors using logistic regression modeling, GLA-P patients were 26% less likely to have a hypoglycemic event during the 1-year follow-up (adjusted odds ratio [OR] = 0.74, 95% CI = 0.66–0.83; $p < 0.0001$), and 49% less likely to have an inpatient/ED hypoglycemic event (adjusted OR = 0.51, 95% CI = 0.42–0.61; $p < 0.0001$) than GLA-V patients.
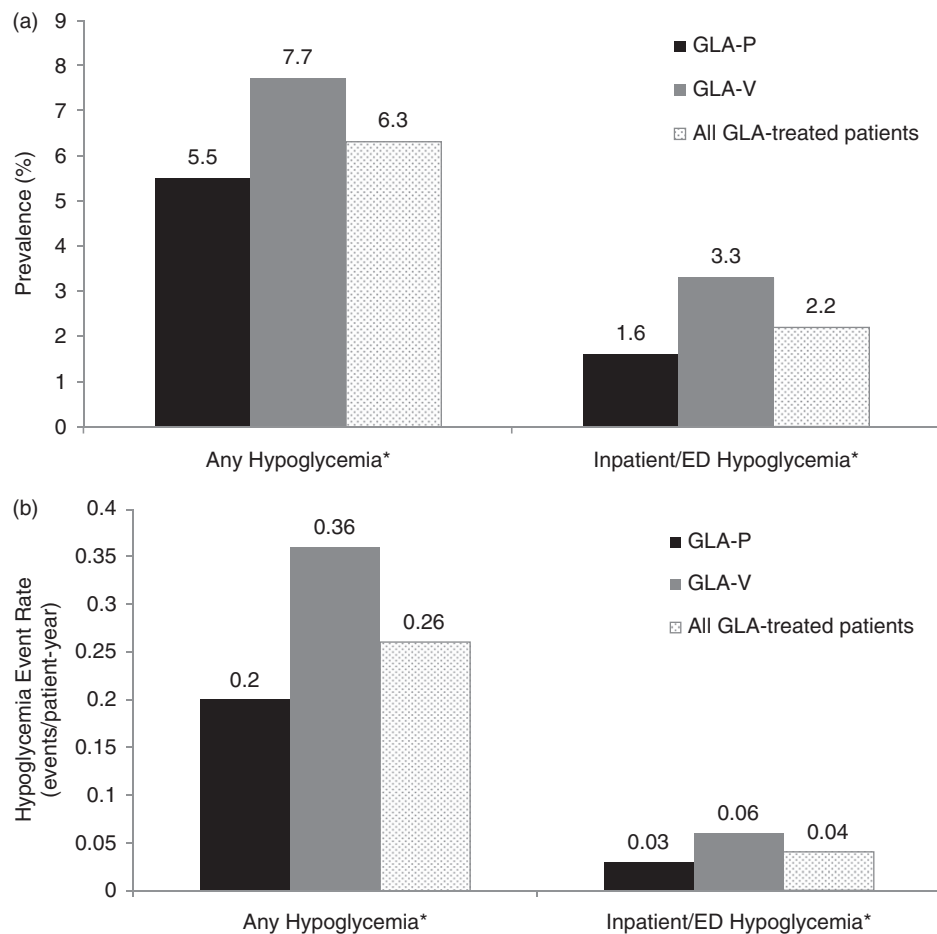
Figure 1. Annual prevalence rate (a) and event rate (b) of hypoglycemia. *$p < 0.0001$ for GLA-P vs GLA-V. ED, emergency department; GLA, insulin glargine; GLA-P, insulin glargine with disposable pen; GLA-V, insulin glargine with vial and syringe.

Baseline characteristics that were associated with a significantly increased risk of any hypoglycemia were CCI, hypoglycemia, neuropathy, and severe mental illness (Table 2); CCI, neuropathy, and nephropathy also predicted a significantly increased risk of inpatient/ED hypoglycemia. In contrast, previous use of metformin (OR = 0.86; 95% CI = 0.75–0.99; $p = 0.0307$) predicted a significantly reduced risk of any hypoglycemia (Table 2).

Negative binomial regression analysis was used to determine any relationship between baseline characteristics and the number of hypoglycemic events. After adjusting for other confounding factors, GLA-P patients had significantly fewer hypoglycemia events compared with GLA-V patients: 0.14 vs 0.22 estimated hypoglycemic events per patient-year ($p < 0.0001$) and 0.02 vs 0.04 estimated inpatient/ED hypoglycemic events per patient-year ($p < 0.0001$).

Baseline characteristics that were significantly and positively correlated with the number of any hypoglycemic events were CCI, hypertension, retinopathy, and neuropathy (Table 3); CCI, retinopathy, and neuropathy

were also positively correlated with the number of inpatient/ED hypoglycemic events.

Baseline hypoglycemia was also significantly correlated with the number of any hypoglycemic events during follow-up. However, the severity of hypoglycemia at baseline only played a role when predicting the number of inpatient/ED hypoglycemic events during follow-up (Table 3).

Previous metformin and exenatide use were negatively correlated with the number of any hypoglycemic events as well as with the number of inpatient/ED hypoglycemic events, while previous sulfonylurea use showed a positive correlation with the number of any hypoglycemic events only (Table 3).

Discussion

This study evaluated the prevalence and event rates of hypoglycemia and related costs in real-world settings among patients initiating insulin therapy with GLA-P or
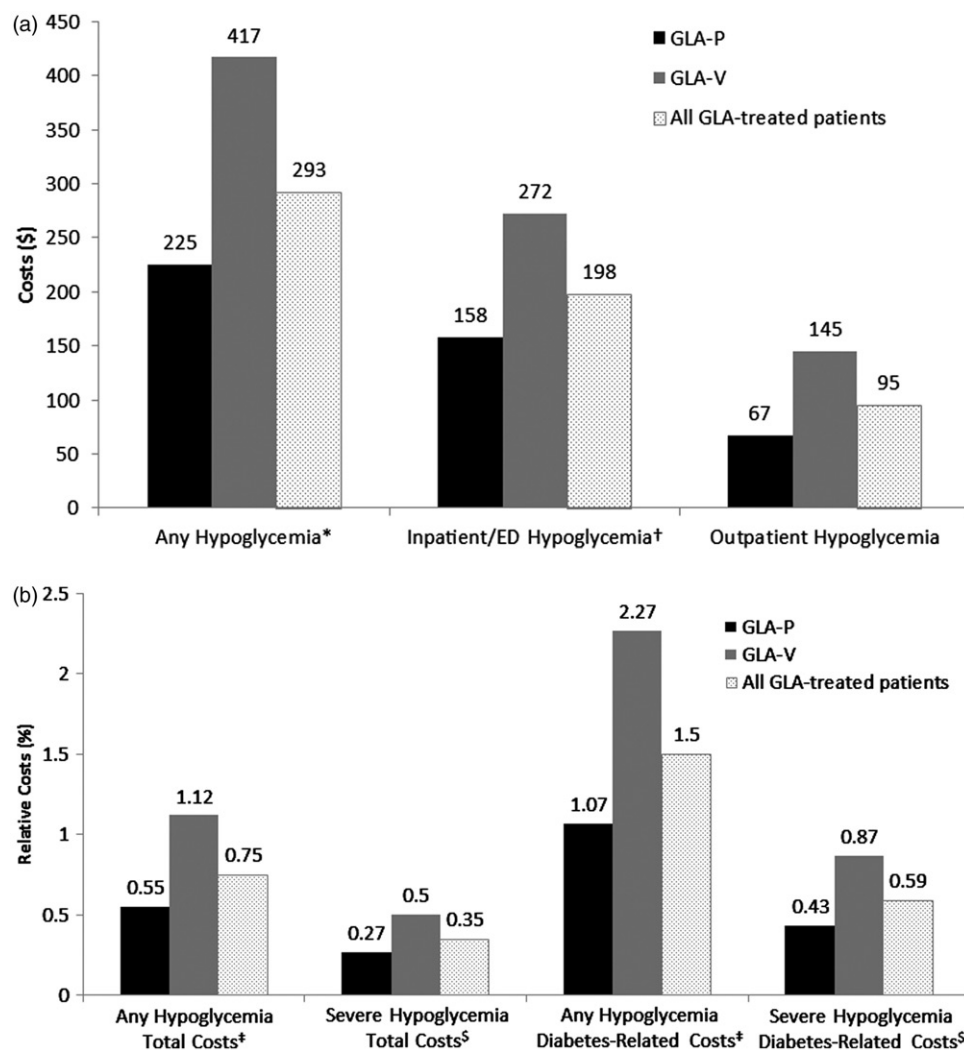
Figure 2. Associated absolute (a) and relative costs (b) of hypoglycemia. (a) Data are presented as costs associated with any hypoglycemia or inpatient/ED hypoglycemia. (b) Data are presented as percentage of total costs or of diabetes-related costs. *p*-values for between-group comparison GLA-P vs GLA-V: *$p = 0.001$; †$p = 0.02$; ‡$p < 0.0001$; $$p = 0.0003$. ED, emergency department; GLA, insulin glargine; GLA-P, insulin glargine with disposable pen; GLA-V, insulin glargine with vial-and-syringe.

GLA-V. Patient-level information was evaluated from six retrospective observational studies that each investigated the medical and economic outcomes of initiating insulin glargine in adult T2DM patients enrolled in US health plan administrative claims databases. Our findings show that patients initiating insulin glargine treatment had low rates of hypoglycemia, which contributed to just 0.75% of the cost of total health-related claims during 1-year follow-up, and 1.50% of the cost of diabetes-related health claims. Furthermore, initiating insulin glargine with a disposable pen device was found to be associated with significantly lower rates of hypoglycemia, and significantly lower hypoglycemia-related total and diabetes-related costs compared with vial-and-syringe. Importantly, these findings relate only to those hypoglycemic events and costs captured in the claims database.

Under-reporting of hypoglycemia by patients may lead to reduced numbers of recorded hypoglycemic events in the claims database[23]. Furthermore, mild hypoglycemic events are not captured, but may be associated with substantial economic consequences to patients, including time away from work and increased costs associated with glucose monitoring after the event[10]. As reported by Brod et al.[10], the economic burden of mild hypoglycemic events was estimated to be $55.16 in the US per event due to work absenteeism and productivity loss. The total average monthly out-of-pocket costs required to manage mild hypoglycemic events was estimated to be $35.36 per month for US patients[10]. Since we observed an association of the use of the pen device with reducing hypoglycemic events severe enough to be recorded in the claims database compared with vial-and-syringe, also milder events may be

Table 2. Logistic regression model for predictors of hypoglycemia.

Parameter	Any hypoglycemia		Inpatient/ED hypoglycemia	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.00 (1.00, 1.01)	0.2245	1.00 (0.99, 1.01)	0.6126
Female	0.92 (0.83, 1.03)	0.1643	0.87 (0.73, 1.05)	0.1477
Group: GLA-P vs GLA-V	0.74 (0.66, 0.83)	<0.0001	0.73 (0.65, 0.81)	<0.0001
Baseline hypoglycemia				
Any inpatient/ED hypoglycemia vs. no hypoglycemia	6.55 (5.03, 8.53)	<0.0001	10.08 (7.34, 13.83)	<0.0001
Outpatient hypoglycemia vs. no hypoglycemia	7.65 (6.30, 9.29)	<0.0001	2.86 (2.00, 4.10)	<0.0001
Comorbidity				
CCI	1.08 (1.04, 1.13)	<0.0001	1.10 (1.04, 1.17)	0.0011
Hypertension	1.05 (0.94, 1.19)	0.3857	0.98 (0.81, 1.19)	0.8541
Hyperlipidemia	0.98 (0.87, 1.10)	0.7460	0.85 (0.71, 1.03)	0.1028
Retinopathy	1.20 (0.99, 1.45)	0.0602	1.22 (0.90, 1.65)	0.2041
Neuropathy	2.26 (1.95, 2.62)	<0.0001	2.43 (1.94, 3.05)	<0.0001
Nephropathy	1.26 (0.99, 1.59)	0.0606	1.54 (1.09, 2.18)	0.0143
Severe mental illness	1.31 (1.03, 1.67)	0.0272	1.36 (0.94, 1.97)	0.1082
Anti-diabetes drugs				
Metformin	0.86 (0.75, 0.99)	0.0307	0.82 (0.66, 1.01)	0.0633
Sulfonylureas	1.09 (0.97, 1.24)	0.1501	1.00 (0.82, 1.21)	0.9846
Thiazolidinediones	0.98 (0.88, 1.10)	0.7601	0.91 (0.76, 1.10)	0.3369
Sitagliptin	1.00 (0.87, 1.15)	0.9959	1.01 (0.80, 1.27)	0.9650
Exenatide	0.86 (0.73, 1.00)	0.0553	0.79 (0.61, 1.03)	0.0859

CCI, Charlson comorbidity index; CI, confidence interval; OR, adjusted odds ratio; GLA-P, insulin glargine with disposable pen; GLA-V, insulin glargine with vial and syringe. The model controlled for health plan type, baseline use of meglitinides, and alpha-glucosidase.

Table 3. Negative binomial regression model of numbers of hypoglycemic events.

Parameter	Any hypoglycemia		Inpatient/ED hypoglycemia	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Age	0.00 (−0.01, 0.00)	0.3293	0.00 (−0.01, 0.01)	0.6578
Female	−0.30 (−0.46, −0.15)	0.0001	−0.14 (−0.37, 0.08)	0.2032
Group: GLA-P vs GLA-V	−0.44 (−0.60, −0.28)	<0.0001	−0.73 (−0.95, −0.51)	<0.0001
Baseline hypoglycemia				
Any inpatient/ED hypoglycemia vs. no hypoglycemia	1.98 (1.37, 2.59)	<0.0001	2.01 (1.31, 2.71)	<0.0001
Outpatient hypoglycemia vs. no hypoglycemia	2.35 (1.91, 2.80)	<0.0001	0.33 (−0.29, 0.94)	0.2964
Comorbidity				
CCI	0.22 (0.15, 0.29)	<0.0001	0.17 (0.08, 0.27)	0.0003
Hypertension	0.19 (0.03, 0.36)	0.0178	0.19 (−0.03, 0.42)	0.0902
Hyperlipidemia	0.00 (−0.16, 0.16)	0.9928	−0.20 (−0.42, 0.03)	0.0872
Retinopathy	0.49 (0.20, 0.77)	0.0008	0.55 (0.18, 0.92)	0.0035
Neuropathy	1.01 (0.76, 1.27)	<0.0001	0.91 (0.58, 1.24)	<0.0001
Nephropathy	−0.18 (−0.56, 0.21)	0.3694	0.17 (−0.33, 0.67)	0.5122
Severe mental illness	0.12 (−0.25, 0.50)	0.5208	0.22 (−0.30, 0.73)	0.4059
Anti-diabetes drugs				
Metformin	−0.37 (−0.56, −0.18)	0.0002	−0.52 (−0.78, −0.25)	0.0001
Sulfonylureas	0.24 (0.07, 0.40)	0.0047	−0.01 (−0.24, 0.22)	0.9431
Thiazolidinediones	−0.01 (−0.16, 0.15)	0.9407	0.04 (−0.19, 0.26)	0.7338
Sitagliptin	−0.03 (−0.22, 0.16)	0.7806	0.07 (−0.20, 0.35)	0.5988
Exenatide	−0.36 (−0.57, −0.15)	0.0007	−0.30 (−0.61, 0.00)	0.0494

CCI, Charlson comorbidity index; CI, confidence interval; GLA-P, insulin glargine with disposable pen; GLA-V, insulin glargine with vial and syringe. The model controlled for health plan type, baseline use of meglitinides, and alpha-glucosidase.

reduced with the improved glycemic control afforded when pen devices are used to administer insulin.

Unlike the individual studies that used propensity score matching to remove observed patient selection bias at baseline[14–19], this study pooled patient-level data from two unmatched cohorts of patients that, although broadly comparable, resulted in significant and potentially clinically relevant differences in baseline characteristics. Therefore, multivariate regression analyses were used to adjust for these differences. Both bivariate and multivariate analyses yielded similar results. Despite these differences, the pooled analysis revealed similar findings in relation to hypoglycemia prevalence and event rates and related costs to those observed in the individual studies

(data not shown). In each of the six studies, initiating insulin glargine with a disposable pen was associated with greater treatment adherence and/or persistence without an increase in costs when compared with exenatide[17], FlexPen[14], and GLA-V[14,17,18]. Moreover, the prevalence and event rates of hypoglycemia in GLA-P initiators was similar to exenatide[19] and FlexPen[16], and significantly lower than with GLA-V[14,17,18].

The large patient sample used in this analysis enabled investigation of the relationship between baseline characteristics in the overall population (i.e., GLA-P and GLA-V patients) and hypoglycemia. Baseline characteristics that were positively correlated with hypoglycemic events included CCI, retinopathy, and neuropathy. Of note, the high incidence of neuropathy and retinopathy at baseline (8.6% and 7.1%, respectively) in the sample may indicate advanced diabetes disease among the patients in the analysis, as does the high baseline HbA1c (9.34%). Based on these data, it would appear that patients who have already experienced microvascular complications due to inadequate glycemic control at the time of initiating insulin therapy may be at higher risk of hypoglycemia. This may point to possible clinical inertia in the treatment of T2DM in the US, which has also been associated with macrovascular complications[24]. These findings are consistent with the findings from a previously published analysis of a large US administrative claims database in which the presence of individual micro- and macrovascular complications of diabetes increased the relative rate of hypoglycemia[22]. In addition, among patients who had both baseline and 1-year follow-up HbA1c data available, HbA1c reduction was associated with a significantly increased risk of hypoglycemia. Multivariate analysis in this sub-sample also showed that higher baseline HbA1c was associated with significantly increased hypoglycemia rates during the follow-up period ($p = 0.023$). Hypoglycemia at baseline also strongly predicted hypoglycemia during follow-up.

Interpretation of the data from the current analysis is limited by the use of unmatched cohorts, as discussed above. Because this is a retrospective analysis, causality between treatment delivery and differences in outcomes could not be established. Blood glucose data was not available, and identification of hypoglycemia events was based on ICD-9-CM codes in the claims data and was, therefore, subject to coding error. The use of ICD-9-CM codes may over- or under-estimate hypoglycemia and the associated costs; the ICD-9-CM codes for hypoglycemia used in all the pooled studies were based on those published by Zhao et al.[21], which were less stringent than the ICD-9-CM code-based algorithm published by Ginde et al.[25]. Therefore, it is possible that our studies over-estimated the hypoglycemia rates. The true rate of hypoglycemia among the patients analyzed in our study may, however, be higher than that recorded in the claims database. Mild or self-treated events, for example, would not have been captured, and under-reporting of hypoglycemia by patients may also lead to reduced numbers of recorded hypoglycemic events in the claims database[23]. It has been shown that observational studies rely on methods that are inadequate for identifying all possible adverse events[26], suggesting that hypoglycemia event rates reported from claims databases may not provide sufficient information on hypoglycemia events compared to clinical trials, in which all instances of hypoglycemia are captured. In our study, due to a lack of glucose reading, we used the setting of hypoglycemia diagnosis as proxy of severity, with inpatient/ED hypoglycemia indicating severe hypoglycemia. This may result in further under-reporting of severe hypoglycemia rates, and may explain why in this analysis higher frequency of inpatient/ED hypoglycemia was not significantly associated with a higher HbA1c reduction. In addition, since milder hypoglycemia and other adverse events are not captured by the claims database, and these may involve costs for the patient, these would not be included in the cost analyses either. Since HbA1c data were not available for all patients in the pooled analysis, an additional limitation is that the association between hypoglycemia and HbA1c levels could only be examined in a sub-group of the study population. Finally, information analyzed for this study was based on data collected from a US managed care population. As a result, these data may not be representative of other populations, and the conclusions may not be appropriately generalized to all patients with T2DM. In particular, the results of this analysis of US data may not apply to patients with T2DM in Europe where use of the pen devices for insulin injections is higher[27], where insulin is added to treatment regimens at an earlier stage, and reimbursement differences exist.

Conclusion

Patients initiating insulin glargine treatment showed low rates of hypoglycemia, especially when using a disposable pen device. Hypoglycemia-related costs were low, contributing a very small proportion to overall and diabetes-related healthcare costs. Certain baseline patient characteristics were associated with increased risk of hypoglycemia.

Transparency

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