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ORIGINAL ARTICLE

Safety of once-daily insulin detemir in patients with type 2 diabetes treated with oral hypoglycemic agents in routine clinical practice

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Abstract

Background: The aim of the present study was to identify demographic and treatment factors that were predictive of hypoglycemia in a large cohort of type 2 diabetic patients initiating insulin detemir.

Methods: The present 24-week observational study of insulin initiation included 17 374 participants from 10 countries. Severe hypoglycemia was defined as an event requiring third party assistance; minor hypoglycemia was defined as a daytime or nocturnal glucose measurement <3.1 mmol/L.

Results: Prior to initiating insulin therapy, 4.9% of the cohort reported hypoglycemia (pre-insulin hypoglycemia), with most (94.2%) reporting minor events and 9.6% reporting severe events. Compared with patients without pre-insulin hypoglycemia, those with pre-insulin hypoglycemia had a higher incidence of events of minor hypoglycemia (1.72 vs 4.46 events per patient-year [ppy], respectively), nocturnal hypoglycemia (0.25 vs 1.09 events ppy, respectively), and severe hypoglycemia (<0.01 vs 0.04 events ppy, respectively) at final visit. Age ($P < 0.047$), body mass index ($P < 0.001$), a prior history of microvascular disease ($P < 0.001$), pre-insulin hypoglycemia ($P < 0.001$), increased number of oral hypoglycemic agents (OHAs; $P < 0.001$), OHA intensification ($P < 0.001$), and the use of glinides ($P = 0.004$) were all found to be independently associated with the occurrence of hypoglycemia during the study.

Conclusions: Once-daily insulin detemir therapy was safe and effective, and rates of hypoglycemia were low. Concerns about hypoglycemia should not deter the initiation of basal insulin analogs.

Keywords: ambulatory care, basal insulin, oral hypoglycemic agent, sulfonylurea, type 2 diabetes mellitus.

Significant findings of the study: A previous history of hypoglycemia or microvascular disease, age <65 years, body mass index <25 kg/m^2, a higher number or intensification of concomitant oral hypoglycemic agents, and glinide use were associated with a significantly higher risk of hypoglycemia following basal insulin initiation.
What this study adds: This large study of basal insulin initiation in patients with type 2 diabetes showed that the overall risk of hypoglycemia was low, and identified several modifiable risk factors that may guide physicians in minimizing hypoglycemia risk during insulin initiation.

Introduction

Insulin is the most effective therapeutic agent for obtaining and maintaining glycemic control in patients with type 2 diabetes (T2D). However, patients and physicians are often discouraged from initiating insulin therapy because of concerns about the increased risk of hypoglycemia.[1] This is particularly true if patients have already experienced hypoglycemia while receiving treatment with oral hypoglycemic agents (OHAs).[2] In addition, although physicians are in general agreement that the benefits of insulin in terms of preventing or delaying complications outweigh the risks, there is a lack of consensus when applying insulin initiation criteria to specific patients.[3] Consequently, patients often continue on inadequate oral therapy for years, and the subsequent delay in initiating insulin therapy may also predispose to irreversible macro- and microvascular damage.[4]

Hypoglycemia is the most common side effect associated with insulin treatment, and although specific risk factors have been identified, these events are often unpredictable. Most episodes occur in the absence of any obvious antecedent cause.[5] Recurrent hypoglycemic episodes may also predispose to the development of hypoglycemic unawareness, which is also a risk factor for the development of more frequent and severe episodes of hypoglycemia.[6–8]

In recent years, results from cardiovascular outcome studies have increased concerns about the risks of hypoglycemia and the impact that episodes of severe hypoglycemia may have on morbidity and mortality. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial showed a paradoxical increase in all-cause mortality in more intensively treated patients.[9] Although the incidence of severe hypoglycemia was higher in this group, the post hoc analyses did not show a clear correlation between these episodes of hypoglycemia and mortality.[10,11] However, suspicion that hypoglycemia was in some way responsible for the deaths remains.[12]

In the present analysis of Study of Once-Daily Levemir (SOLVE), we examine demographic and treatment parameters as risk factors for the occurrence of hypoglycemia during the initiation of basal insulin in people with T2D receiving concomitant OHA therapy in a routine clinical practice setting.

Methods

Subjects

SOLVE was a 24-week observational, multicenter, open-label, prospective study of people with T2D currently receiving one or more OHAs in 10 countries: Canada, China, Germany, Israel, Italy, Poland, Portugal, Spain, Turkey and the UK.[13,14]

Patients were enrolled in the study on a consecutive basis at the discretion of the investigator once the clinical decision to initiate once-daily basal insulin as an add-on to existing OHA therapy had been made. Inclusion criteria differed slightly across the participating countries in order to accommodate local regulations. In Canada, Germany, Poland, and Portugal, patients were included when once-daily insulin detemir was added to current OHA treatment. In the UK, patients who met the eligibility criteria up to 3 months prior to the date of local regulatory approval could also be included retrospectively. In China, patients could have received additional bolus insulin within 4 weeks of recruitment. In Israel, patients could be included within 2 weeks of initiating insulin detemir, and, in Italy, any patient currently treated with insulin detemir could participate. In Spain and Turkey, patients initiating any once-daily basal insulin within the past month or a basal insulin analog within the past 3 months, respectively, were eligible for inclusion.

Pregnant or breast-feeding patients, female patients intending to become pregnant within the next 6 months or those not using adequate contraceptive methods, and children below the age of 6 years were excluded from the study. Pregnancy or the intention to become pregnant were also considered withdrawal criteria. Grounds for withdrawal also included patients discontinuing OHA treatment, adding short-acting insulin, or injecting insulin detemir more than once a day.

Data were collected around three time points: before and 12 and 24 weeks after insulin initiation. Measurements were obtained from values recorded nearest to these time points. The pre-insulin data were obtained retrospectively from medical records. There were no study-prescribed procedures. Any procedures conducted during the study (including recommendations regarding diet and exercise) were at the discretion of the participating physician and in accordance with routine clinical care.

The primary endpoint of the study was to record the incidence of any severe adverse drug reactions (SADRs), including severe hypoglycemia, while using once-daily insulin detemir during routine clinical practice conditions. The incidence of severe, minor, and nocturnal hypoglycemia, as well as glycemic control (as measured by HbA1c and fasting blood glucose [FBG]), were included as secondary endpoints. A glucose measurement <3.1 mmol/L (56 mg/dL) with or without symptoms was considered to be a minor hypoglycemic event; severe hypoglycemia was defined as an event requiring

third party assistance. Any episode occurring between bedtime and awakening the next morning was considered to be a nocturnal event. Severe hypoglycemia was recorded as events recalled within the preceding 12 weeks in all countries (with the exception of the UK, where this time frame was within the preceding 4 weeks). This reflected a difference in the reporting protocol between the UK and other countries. Minor hypoglycemia was recorded as events recalled within the preceding 4 weeks in all countries.

Statistical analysis

Continuous variables are summarized with descriptive statistics (mean ± SD). Discrete variables are reported in frequency tables. Hypoglycemic events are reported as events per patient-year (ppy).

Statistical comparisons of pre- and post-initiation on insulin detemir were performed with paired *t*-tests for continuous variables. The Wilcoxon signed-rank test was used to compare the number of hypoglycemic events before insulin and at final visit.

Exploratory analyses of risk factors for the development of one or more hypoglycemic events during the study were performed using logistic regression. Predictor variables included age, gender, ethnicity, body mass index (BMI), duration of diabetes, concomitant diabetes medications, insulin dose, a previous history of hypoglycemia, and pre-existing macro- and microvascular diabetic complications. The model was built from a basic model comprised of the parameters patient age, gender, duration of diabetes, pre-insulin HbA1c and BMI. Other demographic and treatment effects were evaluated adjusting for the parameters in the basic model. The effects of a change to the OHA regimen and individual OHAs were additionally adjusted for the number of prescribed OHAs. A final model was constructed by evaluating all parameters (including a parameter to denote OHA regimen intensification, reduction or no change) using a process of backward elimination (selection criteria $P < 0.05$). All testing used two-sided tests with the criteria set at $\alpha = 0.05$. Missing data were not imputed.

Due to the fact that groups were non-randomized and the potential risk of confounding, we do not report *P*-values for inter-group comparisons.

Results

A total of 17 374 patients was included in the analysis (Table 1). During the study, HbA1c improved from 8.9 ± 1.6% to 7.5 ± 1.2% (change –1.3 ± 1.5%; $P < 0.001$) and FBG improved from 10.1 ± 3.0 to 7.1 ± 1.8 mmol/L (change –3.1 ± 3.0 mmol/L; $P < 0.001$).

There was a corresponding increase in the proportion of patients reporting at least one episode of minor hypoglycemia from 4.7% prior to insulin initiation to 6.2% at the end of the study. This increase was due largely to an increase in the incidence of minor hypoglycemia, which increased from 1.58 to 1.83 events ppy at the end of the study ($P < 0.001$). There was no significant increase in the incidence of nocturnal hypoglycemia between pre-insulin and the final visit (0.27 vs 0.28 events ppy, respectively; $P = 0.08$), but there was a significant decrease in the incidence of severe hypoglycemia, from 0.04 events ppy before insulin to <0.01 events ppy at the end of the study ($P < 0.001$). Overall, the proportion of patients reporting an episode of severe or minor hypoglycemia at any point during the study was low: 0.1% for severe hypoglycemia and 11.2% for minor hypoglycemia.

Severe hypoglycemia

The characteristics of patients experiencing one or more episodes of severe hypoglycemia before and after the initiation of insulin therapy are given in Table 1.

Patients with severe pre-insulin hypoglycemia appeared to have lower HbA1c (8.4 ± 1.5% vs 8.9 ± 1.6%) and FBG values (9.2 ± 3.0 vs 10.3 ± 3.1 mmol/L) relative to the total cohort. In contrast, the small group of patients reporting severe hypoglycemia during the study ($n = 19$) tended to have worse glycemic control prior to insulin initiation compared with the total cohort (HbA1c 9.4 ± 2.4% vs 8.9 ± 1.6%, respectively; FBG 11.0 ± 6.9 vs 10.3 ± 3.1 mmol/L, respectively). Patients with severe hypoglycemia at any time before or during the study had a longer duration of diabetes and a higher proportion had a history of microvascular disease (52.9% and 52.6%, respectively) relative to the total cohort (33.0%). The proportion of patients using sulfonylureas with severe hypoglycemia during the study also appeared to be higher relative to the total cohort (77.8% vs 59.3%, respectively).

Pre-insulin hypoglycemia

Information regarding a previous history of hypoglycemia prior to insulin initiation (pre-insulin hypoglycemia) was available for 17 338 (99.8%) patients (Table 1).

Of the 4.9% patients with pre-insulin hypoglycemia, 94.2% experienced one or more minor events, with 9.6% experiencing severe hypoglycemia. Patients with pre-insulin hypoglycemia had a higher incidence of any minor (4.46 vs 1.72 events ppy), nocturnal (1.09 vs 0.25 events ppy) and severe hypoglycemia (0.04 vs <0.01 events ppy) during the study compared with patients without pre-insulin hypoglycemia. One individual experienced recurrent severe hypoglycemia.

Table 1 Baseline patient demographics and treatment (total cohort and according to (a) the presence of severe hypoglycemia pre-insulin or during the course of the study, and (b) the presence or absence of hypoglycemia prior to insulin initiation (pre-insulin hypoglycemia)

		Severe hypoglycemia		Pre-insulin hypoglycemia	
	Total cohort	Pre-insulin	During study†	Present	Absent
No. patients (%)	17 374	85	19	849 (4.9%)	16 489 (95.1%)
Age (years)	62 ± 12	62 ± 12	67 ± 12	61 ± 12	62 ± 11
% Men	53%	55%	61%	53%	53%
Duration of diabetes (years)	10 ± 7	11 ± 8	14 ± 10	10 ± 8	10 ± 7
Weight (kg)	80.9 ± 17.7	80.6 ± 18.9	80.8 ± 16.1	78.0 ± 16.6	81.0 ± 17.6
FBG (mmol/L)	10.3 ± 3.1	9.2 ± 3.0	11.0 ± 6.9	9.3 ± 2.7	10.2 ± 3.0
HbA1c (%)	8.9 ± 1.6	8.4 ± 1.5	9.4 ± 2.4	8.4 ± 1.5	8.9 ± 1.6
Previous medical history					
Microvascular disease	33.0%	52.9%	52.6%	43.4%	32.4%
Macrovascular disease	26.6%	31.0%	27.8%	33.0%	26.3%
Number of OHAs					
One	29.9%	33.3%	27.8%	28.8%	29.9%
Two	54.1%	44.4%	50.0%	53.6%	54.1%
Three or more	16.0%	22.2%	22.2%	17.7%	16.0%
Types of OHAs					
Biguanides	81.3%	66.7%	83.3%	75.9%	81.6%
Sulfonylureas	59.3%	59.3%	77.8%	60.9%	59.3%
Glinides	16.1%	25.9%	5.6%	21.3%	15.8%
α-Glucosidase inhibitors	12.2%	17.3%	5.6%	15.0%	11.7%
Thiazolidinediones	12.1%	18.5%	16.7%	12.7%	12.1%
DPP-4 Inhibitors	6.5%	8.6%	5.6%	4.6%	6.6%
Other	0.1%	1.2%	0.0%	0.4%	0.1%

Unless indicated otherwise, data are given as the mean ± SD.
†Represents baseline patient demographics for those who later experienced severe hypoglycemia during the study.
DPP-4, dipeptidyl peptidase-4; FBG, fasting blood glucose; OHA, oral hypoglycemic agent.

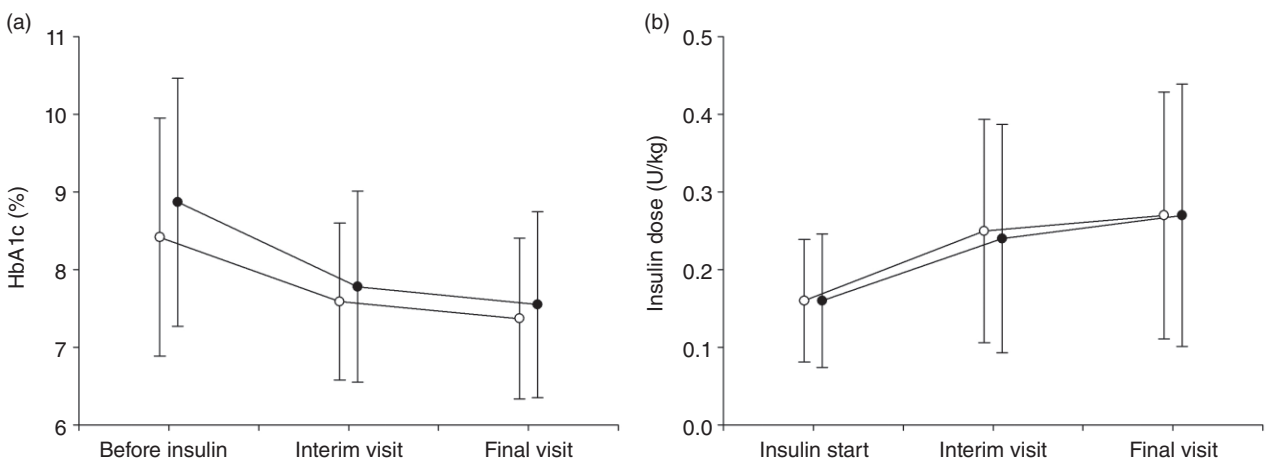

Figure 1 Change in (a) HbA1c and (b) insulin dose according to the presence (○) or absence (●) of hypoglycemia prior to insulin initiation. Data are given as the mean ± SD.

Mean HbA1c was lower in the group with pre-insulin hypoglycemia (Fig. 1a), but insulin start dose and subsequent titration were similar regardless of a previous history of hypoglycemia (Fig. 1b).

In general, there were decreases in the proportion of patients prescribed sulfonylureas, thiazolidinedione, and dipeptidyl peptidase-4 inhibitors at the time of insulin initiation, but an increase in the proportion of

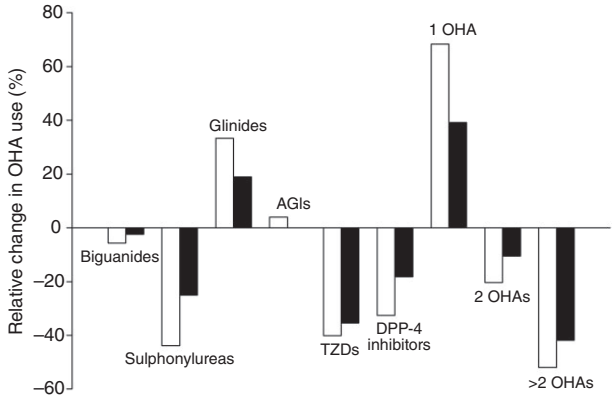

Figure 2 Percentage change in prescribed oral hypoglycemic agents (OHAs; final visit relative to before the initiation of insulin) according to the presence (□) or absence (■) of hypoglycemia prior to insulin initiation. AGIs, α-glucosidase inhibitors; TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4.

patients using glinides (Fig. 2). These trends were more pronounced in patients with a previous history of hypoglycemia.

Risk factors for hypoglycemia

Models used to analyze the influence of demographic and study treatment parameters on the occurrence of hypoglycemia during the study are given in Table 2.

In the final backward elimination model, the following covariates remained independent predictors of hypoglycemia during the study: decreasing age (significantly decreased odds ratio [OR] for all age groups ≥65 years relative to age <50 years), decreasing BMI (significantly decreased for all BMI groups ≥25 kg/m^2 relative to BMI <25 kg/m^2), previous history of microvascular disease (OR 1.34; 95% confidence interval [CI] 1.20–1.50) or hypoglycemia (OR 3.41; 95% CI 2.88–4.04), and increasing number of OHAs (significantly increased OR for patients treated with two [OR 1.52; 95% CI 1.33–1.74] or more than two [OR 1.81; 95% CI 1.51–2.16] OHAs relative to a single OHA), OHA intensification (OR 1.46; 95% CI 1.13–1.89 relative to unchanged OHA regimen), or the use of glinides (OR 1.22; 95% CI 1.07–1.39) at the time of insulin initiation. There was a U-shaped relationship between final insulin dose and risk of hypoglycemia during the study, with final insulin doses of between 38 and 52 IU being associated with an increased risk of hypoglycemia compared with doses ≤38 IU (OR 1.17; 95% CI 1.02–1.35; $P < 0.001$), and with higher doses associated with a similar risk of hypoglycemia as doses ≤38 IU.

Discussion

SOLVE is currently the largest study of basal insulin initiation in patients with T2D. In patients with a previous history of hypoglycemia on OHAs (pre-insulin hypoglycemia), the incidence of recurrent hypoglycemia after the initiation of insulin was low despite clinically significant improvements in glycemic control. Multivariate regression analysis identified younger age (≤65 years), absence of overweight/obesity (BMI ≤25 kg/m^2), a previous history of hypoglycemia or microvascular disease, an increased number or intensification of concomitant OHA therapy, and the use of glinides as significant independent risk factors for any hypoglycemia during the study. The largest increase in risk of any hypoglycemia during the study occurred in patients with a history of hypoglycemia prior to insulin initiation, following adjustment for other model parameters.

The risk of hypoglycemia is an important consideration in determining individual glycemic targets and type of treatment. The most recently published American Diabetes Association guidelines continue to recommend glycemic targets of <7.0%,[15] with a consideration of more stringent control in patients without significant cardiovascular disease provided that these can be achieved without significant hypoglycemia; or less stringent glycemic control in patients with a history of severe hypoglycemia. These guidelines also recognize hypoglycemia as a disadvantage of sulfonylurea, glinide and insulin therapy.

Basal insulin analogs have previously been shown to lower the risk of hypoglycemia with respect to human insulin preparations and more intensive regimens that include rapid-acting insulin preparations.[15–17] The previously reported incidence of hypoglycemia from treat-to-target studies of insulin detemir ranges between 2.3 and 7.5 events ppy (mean HbA1c 7.6%–6.8%) depending on the titration algorithm used.[18–20] The definition of hypoglycemia in these aforementioned studies was a blood glucose level <56 mg/dL (<3.1 mmol/L). Using similar definitions, the reported incidence of hypoglycemia in patients with T2D using insulin glargine and neutral protamine Hagedorn (NPH) was 3.0 and 5.1 events ppy, respectively.[21] The pattern and incidence of severe, minor, and nocturnal hypoglycemia seen in the present study were similar to a previously reported observational study of insulin detemir in insulin-naïve patients with T2D.[22] However, in both observational studies insulin titration was suboptimal, with substantially lower final insulin doses than have been used in randomized controlled trials of similar duration.[23]

The observed rates of severe hypoglycemia were higher prior to insulin initiation than at any time following the

Table 2 Results of logistic regression analyses of demographic and study treatment parameters as risk factors for hypoglycemia during the 24-week study, where risk is expressed as the odds ratio with 95% confidence intervals

Parameter	Category	OR	95% CI		*P*-value
			Lower	Upper	
Basic model					
Age (years)	≥75	0.640	0.509	0.805	0.0250
	70–74	0.734	0.585	0.920	
	65–69	0.784	0.631	0.975	
	60–64	0.801	0.653	0.983	
	55–69	0.800	0.651	0.984	
	50–54	0.851	0.681	1.064	
	<50 (reference group)				
Gender	Female vs male	1.047	0.932	1.176	0.4263
Duration of diabetes (years)	>13	1.372	1.154	1.630	0.0014
	>8.4–13	1.249	1.061	1.470	
	>5–8.4	1.032	0.871	1.222	
	≤5 (reference group)				
Body mass index (kg/m^2)	≥35	0.525	0.428	0.645	<0.0001
	30–34	0.590	0.499	0.696	
	25–29	0.699	0.606	0.805	
	<25 (reference group)				
Pre-insulin HbA1c (%)		1.004	0.970	1.041	0.8067
Adjusted for basic model parameters					
Previous History					
Pre-insulin hypoglycemia	Yes vs no	3.617	3.005	4.352	<0.0001
Macrovascular disease	Yes vs no	1.140	0.996	1.305	0.1630
Microvascular disease	Yes vs no	1.353	1.196	1.531	<0.0001
No. OHAs at insulin initiation	Three or more	1.817	1.512	2.182	<0.0001
	Two	1.522	1.317	1.759	
	One (reference group)				
Adjusted for basic model parameters and no. of OHAs at insulin initiation					
Change in OHA regimen	Increased	1.519	1.120	2.060	<0.0001
	Decreased	1.034	0.884	1.209	
	Unchanged (reference group)				
Metformin	Yes vs no	0.671	0.588	0.766	<0.0001
Sulfonylureas	Yes vs no	0.905	0.801	1.022	0.1073
Glinides	Yes vs no	1.214	1.049	1.406	0.0093
α-Glucosidase inhibitors	Yes vs no	1.022	0.856	1.220	0.8105
Thiazolidinediones	Yes vs no	0.798	0.633	1.005	0.0548
DPP-IV inhibitors	Yes vs no	0.677	0.502	0.913	0.0107
Final insulin dose (IU)	>74	0.899	0.745	1.086	0.0002
	53–74	0.977	0.816	1.171	
	39–52	1.257	1.080	1.464	
	≤38 (reference group)				

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; OHA, oral hypoglycemic agent; OR, odds ratio.

initiation of insulin. Despite a general trend to more severe episodes of hypoglycemia in hospital studies and in clinical trials using aggressive treatment targets, the link between treatment type and severe hypoglycemia remains largely unexplained. Murata et al.[5] reported that the cause was unidentified in the majority of severe hypoglycemic events, and that identified causes were behavioral (e.g. missed meal, dosing error or excessive exercising or dieting), and not related to prescribed changes in treatment. The results of the ACCORD subanalyses also support the notion that the risk of severe hypoglycemia may be attributable to the type and complexity of therapy, rather than the degree of control achieved by the therapy.[10,24]

A number of unknowns and controversies remain surrounding the use of insulin in combination with different OHAs. The effects of insulin in combination with specific OHAs on HbA1c and the risk of hypoglycemia were evaluated using multivariate regression modeling. The model demonstrates an increased risk of hypoglycemia with increasing number of concomitant OHAs, and OHA treatment intensification at the time of insulin initiation. For participants using two and three or more OHAs, the risk of hypoglycemia increased by 52% and 81%, respectively, compared with patients using a single oral agent.

Despite the documented associations between sulfonylureas and increased risk of hypoglycemia,[25] such an association was not identified in the present study. It is possible that because the present study was an observational study, physicians took steps to minimize this perceived increase in risk, either by avoiding the combination of sulfonylurea and insulin, or by preemptively reducing the dose of sulfonylureas and/or the dose of insulin. In the present analysis, the percentage of patients discontinuing sulfonylurea therapy at the time of insulin initiation was twice as high in patients with a history of hypoglycemia than without. There is also some evidence for sulfonylurea and/or insulin dose reduction, because in a previously published analysis sulfonylurea use was found to be associated with a higher end-of-study HbA1c.[26] However, glinides may not have been perceived as carrying the same risk of hypoglycemia as sulfonylureas. Based on these findings, physicians should consider discontinuing sulfonylurea or glinide therapy at the time of insulin initiation.

There are a number of limitations of the present study. Because the present study was an observational study, it is not possible to exclude a study effect, although these effects are typically small in relation to the changes in glycemic efficacy reported here. Documenting of blood glucose measurements and hypoglycemia was not compulsory; thus, the reporting of hypoglycemia in the present study was subject to recall bias. As such, the reporting of hypoglycemia is likely to be an underestimation of the true incidence of hypoglycemia, but nevertheless reflects the reporting of hypoglycemia in real-life clinical practice. Furthermore, unless it is assumed that there is a relationship between hypoglycemia reporting and the demographic and clinical parameters reported in this analysis, then the predictors of hypoglycemia identified remain valid. The true incidence of hypoglycemia before and during the study may also have been higher than that recorded as a result of hypoglycemic unawareness.[27] Recall and hypoglycemia unawareness may explain certain associations; for example, the fact that older age was found to be a negative predictor of hypoglycemia.

In conclusion, minor episodes of hypoglycemia occurred more frequently in patients following the introduction of insulin detemir; however, the overall self-reported rates of hypoglycemia remained low. The self-reported incidence of severe hypoglycemia was lower following the initiation of insulin. A previous history of hypoglycemia, more intensive concomitant OHA therapy, and the use of glinides were among the most important risk factors associated with the occurrence of hypoglycemia during the present study. The identification of modifiable risk factors may assist physicians in minimizing hypoglycemia risk while initiating insulin therapy.

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