

## Lower Severe Hypoglycemia Risk: Insulin Glargine Versus NPH Insulin in Type 2 Diabetes

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An abundance of data demonstrates that intensive glycemic control can preclude or delay chronic complications of diabetes.<sup>1-6</sup> Accordingly, intensive diabetes therapy that targets near-normal blood glucose levels is recommended by the American College of Endocrinology/American Association of Clinical Endocrinologists and the American Diabetes Association.<sup>7,8</sup> Iatrogenic hypoglycemia is an expected and common consequence of this approach to tight glycemic control.<sup>9</sup>

Because of the progressive decline in  $\beta$ -cell function in type 2 diabetes, for many patients insulin therapy will be essential to achieve and maintain glycemic control.<sup>10,11</sup> Although hypoglycemia during insulin therapy has been noted to be “less of a risk in type 2 diabetes compared with type 1 diabetes,”<sup>9</sup> it remains a common concern and can be a major barrier to both initiating and/or advancing insulin therapy.<sup>12</sup> Severe hypoglycemia is generally acknowledged to occur at about one tenth the rate of that in patients with type 1 diabetes who are treated to comparable glycosylated hemoglobin (A1C) levels with multiple daily insulin injections. Basal insulin glargine has demonstrated a lower risk of hypoglycemic events compared with neutral protamine Hagedorn (NPH) insulin in several clinical trials and thus is an important option for overcoming the barrier of hypoglycemia. This difference in hypoglycemic risk between insulin glargine and conventional insulin also has been examined in clinical practice database studies. Another basal insulin analog, insulin detemir, recently was introduced in the United States, although it has been marketed in Europe for more than 2 years. It also appears to have a significantly lower risk of causing hypoglycemia compared with NPH insulin in patients with type 2 diabetes.<sup>13,14</sup> At the time of this writing there were no published medical claims data or data from US clinical practice settings for insulin detemir; however, it will be important to examine these data as they become available.

We provide a brief overview of hypoglycemia in patients with insulin-treated diabetes and focus on the incidence of hypoglycemia associated with insulin glargine in patients with type 2 diabetes in both research and practice settings. Data sources include randomized trials comparing insulin glargine to NPH insulin, clinical practice databases, and medical claims analyses.

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Hypoglycemia is a common consequence of achieving tight glycemic control for patients with type 2 diabetes, with clinical effects ranging from occasional mild discomfort to incapacitation, coma, or in rare cases, death. Severe hypoglycemic events, particularly those resulting in emergency medical intervention or hospitalization, incur substantial medical costs for patients and the healthcare system. Although vigilance is needed for the possibility of severe events, hypoglycemia need not be a barrier to effective glycemic control in type 2 diabetes. Data from clinical trials and meta-analyses have demonstrated that the basal insulin analog insulin glargine results in a reduced rate of severe hypoglycemic events compared with conventional insulin therapy such as neutral protamine Hagedorn (NPH) insulin. Overall, use of insulin glargine compared with NPH insulin appears to reduce the risk of nocturnal and severe hypoglycemia by 40% to 60% and may result in cost savings. Analyses of hypoglycemia rates from “real-world” clinical practice databases and retrospective analyses of medical claims data also have revealed reduced rates with insulin glargine, consistent with the findings from clinical trials.

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**For author information and disclosures, see end of text.**

## OVERVIEW OF HYPOGLYCEMIA

### Definitions and Incidence

Clinical hypoglycemia ranges from mild/moderate events that are easily recognized and reversed by the patient to severe, debilitating events that may require hospitalization. (For a review of hypoglycemia, see *Hypoglycemia, Pathophysiology, Diagnosis, and Treatment*.<sup>9</sup>) Nocturnal hypoglycemia is a common concern, with frequencies of >10% to ~50% reported in the literature (in patients with insulin-treated diabetes<sup>15-17</sup>). Severe (or “major”) events, although relatively uncommon, can cause sufficient patient impairment to necessitate intervention or support from another person.<sup>18</sup> In the extreme, severe hypoglycemic events can lead to neurologic impairment and, in rare but serious cases, seizures, coma, and death.<sup>19</sup>

Comparisons of events across clinical trials can be a challenge because of differences in ascertainment, reporting measures, and methods. Severe hypoglycemia in insulin-treated patients with type 2 diabetes has been explored in both retrospective and prospective studies and has been reported most often as either an incidence rate or a percentage of patients experiencing 1 or more hypoglycemia events per year.<sup>20</sup> In general, the incidence of severe hypoglycemia was lower in prospective studies (0-20 episodes per 100 patient-years) than in retrospective studies (15-73 episodes per 100 patient-years). One of the largest ongoing prospective studies—the United Kingdom Prospective Diabetes Study—recently reported an annual rate of recurrent moderate or severe hypoglycemia of 3.8% to 5.5% in insulin-treated patients with type 2 diabetes.<sup>21</sup> The differences in reported frequency of hypoglycemia between studies may be due to differences in clinical characteristics (eg, age), classification of “severe” episodes, risk-factor profiles, type of insulin regimen and intensity of treatment, duration of illness, and duration of insulin exposure.<sup>20</sup> In fact, during the first 2 years of insulin therapy, severe hypoglycemia rates are low (similar to rates in patients taking sulfonylureas), and hypoglycemic events are considerably less frequent than they are in patients with type 1 diabetes.<sup>11</sup> Furthermore, the rate of severe hypoglycemia in patients with type 2 diabetes has been estimated to be 10% of that in patients with type 1 diabetes, even with intensive insulin therapy.<sup>22</sup>

### Economic Burden

In addition to causing adverse symptoms and, in some cases, morbidity, hypoglycemia results in significant medical expenditures.<sup>23-25</sup> Moderate to severe hypoglycemia con-

tributes to an increased use of healthcare services by insulin-treated patients, including hospitalization, emergency room and office visits, and increased short-term disability leave.<sup>23,24</sup> Researchers who recently assessed the economic effects of hypoglycemia estimated a mean cost per episode of \$1186 and annualized costs of \$3241 per patient with a diagnosis of hypoglycemia.<sup>23,24</sup> Therapies that can provide effective glycemic control with less potential for hypoglycemia may be expected not only to improve medical outcomes, but also to help limit expenditures for healthcare.

## LOWER RATES OF SEVERE HYPOGLYCEMIA WITH INSULIN GLARGINE VS CONVENTIONAL INSULIN

### Randomized Clinical Trials and Meta-analyses

Several randomized clinical trials have demonstrated that the addition of insulin glargine to oral antidiabetic drugs is associated with a significantly lower incidence of hypoglycemia compared with NPH insulin.<sup>26-28</sup> In the Treat-to-Target Trial, patients who had inadequately controlled type 2 diabetes with oral therapy received add-on therapy with either basal insulin glargine or NPH insulin. A forced weekly titration algorithm was used for insulin dose, targeting an A1C goal of  $\leq 7.0\%$ . Results demonstrated that nearly 25% more patients treated with insulin glargine achieved an A1C value of  $\leq 7.0\%$  without nocturnal hypoglycemia compared with those treated with NPH insulin.<sup>26</sup> Further, patients in the glargine group had 21% to 48% lower rates for other categories of symptomatic hypoglycemia. There were 3.0 and 5.1 events per patient-year with a blood glucose measurement of  $< 56$  mg/dL in the insulin glargine and NPH insulin groups, respectively.<sup>26</sup> A post hoc analysis of the severe hypoglycemic events reported in the Treat-to-Target Trial, however, indicated that many episodes reported as severe (defined as requiring third-party assistance and associated with either a glucose level of  $< 56$  mg/dL or prompt recovery after oral carbohydrate, IV glucose, or glucagon) were coded on case report forms as of moderate severity by the investigators when characterizing the event (unpublished data, sanofi-aventis U.S., 2003), suggesting that although third-party assistance was provided, it may not have been required. The majority of these events were quickly corrected with carbohydrates. Moreover, several of the severe events were assessed as possibly avoidable. In another clinical trial comparing bedtime NPH with insulin glargine given either at bedtime or in the morning, the rates of severe hypoglycemia (defined as requiring third-party assistance and associated with either a glucose level of  $< 50$  mg/dL

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■ **Table.** Percentage of Patients Reporting Severe Hypoglycemic Events With Insulin Glargine vs NPH Insulin (Meta-analysis of 4 Randomized Clinical Trials)<sup>27,\*</sup>

Type of Symptomatic Severe Hypoglycemic Events	Insulin Glargine (% of Patients)	NPH Insulin (% of Patients)	P	Significant % Risk Reduction With Insulin Glargine
<b>Severe documented</b>	1.4	2.6	.0442	46
Plasma glucose 72 mg/dL (4.0 mmol/L)	1.1	2.0	.1089	—
Plasma glucose 56 mg/dL (3.1 mmol/L)	0.9	1.5	.1735	—
<b>Severe nocturnal documented</b>	0.7	1.7	.0231	59
Plasma glucose 72 mg/dL (4.0 mmol/L)	0.6	1.5	.0416	60
Plasma glucose 56 mg/dL (3.1 mmol/L)	0.5	1.3	.0461	62

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or prompt recovery after carbohydrate, IV glucose, or glucagon) were 0.12, 0.04, and 0.06 events per patient-year, respectively.<sup>28</sup> Most recently, researchers who compared glimepiride plus insulin glargine with glimepiride plus NPH reported a lower rate of symptomatic nocturnal hypoglycemia (defined as events that occurred during sleep [between bedtime and morning rising]) in patients receiving insulin glargine (1.1 vs 3.1 events per patient-year for NPH;  $P = .001$ ).<sup>29</sup> Rates of severe hypoglycemia were 0.1 versus 0.2 events per patient-year ( $P = .369$ ).

The incidence of severe events was very low in clinical trials; however, meta-analyses can serve to increase statistical power when evaluating such events. A recent meta-analysis by Rosenstock et al combined results from 4 open-label, randomized, parallel, open-group studies comparing insulin glargine with NPH insulin in type 2 diabetes. A significant risk reduction was associated with insulin glargine for severe hypoglycemia (46%,  $P = .0442$ ) and severe nocturnal hypoglycemia (59%,  $P = .0231$ ) (Table).<sup>27</sup> Furthermore, in the subgroup of patients achieving the target A1C level of  $\leq 7.0\%$ , those who were treated with insulin glargine experienced a lower incidence of nocturnal hypoglycemia than those taking NPH insulin (39% vs 49%;  $P < .01$ ); however, the incidence of all other types of hypoglycemia was similar between groups. The collective results from individual clinical trials as well as a meta-analysis support the contention that insulin glargine results in a lower rate of overall, nocturnal, and severe hypoglycemic events compared with NPH insulin.

### Analyses of Clinical Practice Databases

Utilization of clinical practice databases can provide valuable data for evaluation of insulin regimens for diabetes in

usual-care settings.<sup>30,31</sup> Fischer et al conducted a 12-month office-based observational study of patients initiating therapy with insulin glargine in a private endocrinology clinic.<sup>31</sup> Information was collected from patient cohorts with type 1 ( $n = 135$ ) or type 2 ( $n = 180$ ) diabetes. NPH insulin was the prior therapy in approximately 70% of patients. Compared with prior therapies (the year before insulin glargine initiation), insulin glargine (the year after initiation) was associated with significant mean reductions in hypoglycemic episodes in both patients with type 1 ( $-0.33$ ,  $P = .002$ ) and type 2 ( $-0.20$ ,  $P = .004$ ) diabetes. In addition, insulin glargine significantly improved A1C levels compared with prior therapies in this time frame (type 1:  $-0.28\%$ ,  $P = .0307$ ; type 2:  $-0.60\%$ ,  $P < .0001$ ).<sup>31</sup> These findings are consistent with those from another clinical practice database of 292 patients with type 1 diabetes who switched to basal insulin glargine from NPH insulin, Lente, or Ultralente.<sup>30</sup> The rate of severe hypoglycemic events per patient per year declined from 1.3 in the 1-year period preceding initiation of glargine to 0.57 in the year after initiation of glargine.<sup>30</sup> The analysis of clinical practice databases may be more representative of real-world settings.

It must be kept in mind, however, that these data are uncontrolled and may not capture other interventions or changes that may have occurred in patient management beyond the change in insulin. Although direct comparisons between studies must be made with caution because of differences in methodology (eg, definitions of hypoglycemia, ascertainment), the available clinical practice data appear consistent with clinical trial data and provide additional support for the observation that insulin glargine is associated with less overall and less severe hypoglycemia than conventional insulins.

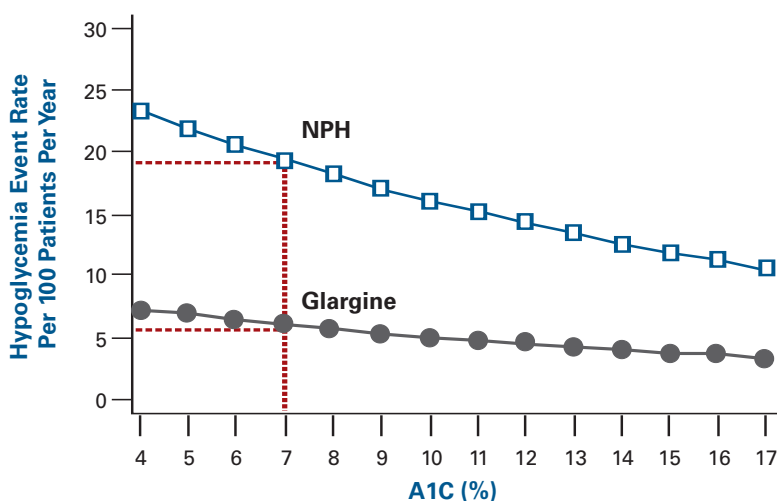
### Analysis of Medical Claims Data

Insurance claims data provide another important source for evaluating not only the incidence of severe hypoglycemic events, but also their economic impact. However, because these data generally are derived from claims for emergency departments, hospitalizations, physician visits, and ambulance calls, the rates are lower than those in other population-based assessments. Bullano et al retrospectively examined pharmacy and medical claims data from a southeastern US managed healthcare plan for patients who initiated therapy with either insulin glargine (n = 310) or NPH insulin (n = 1124).<sup>32</sup> The events in this analysis are believed to be severe, as such events are more likely to generate insurance claims. Analysis of hypoglycemia-related claims before (preindex period) and after (postindex period) initiation of insulin revealed that the rate of events (per 100 patients per year) declined from 30 to 10 among patients who initiated therapy with insulin glargine, whereas that for patients starting NPH insulin increased slightly, from 29 to 31. Negative binomial regression was used to predict rates of patient hypoglycemic events at A1C levels between 4% and 17% (Figure). At an A1C level of 7.0%, the rate of events per 100 patients per year was estimated to be 7.3 for insulin glargine and 18.3 for NPH insulin (P = .009); thus, to avoid 1 hypoglycemic event per patient per year, 9 patients would need to be treated with insulin glargine rather than NPH insulin. The mean annual medication cost of insulin glargine was \$390, with a mean annual dif-

ference in cost between insulin glargine and NPH insulin of \$47. Because the mean cost per hypoglycemic event was \$1087, it is worthwhile to note that the cost increase associated with treating 9 patients with insulin glargine versus NPH insulin (ie, \$423) was \$664 less than the cost of treating 1 hypoglycemic event.<sup>32</sup>

Zhang and Menditto, who conducted a retrospective review of claims from Medicaid recipients in California, also report reductions in hypoglycemia-related claims after introduction of insulin glargine.<sup>33</sup> A total of 267 patients using insulin glargine were matched to 534 reference patients to assess short-term costs of diabetes care before and after initiation of therapy with insulin glargine. Hypoglycemia-related inpatient claims decreased in the insulin glargine group, but remained unchanged in the reference group. Hypoglycemia-related emergency department claims declined similarly in both groups. Initiation of insulin glargine was associated with reduced costs at 6 months from baseline, including inpatient and total costs of diabetes-related care and expenditures from inpatient hypoglycemia-related claims.<sup>33</sup> Consistent with these data, a recent analysis of patient-level data from Medicaid programs in 4 states demonstrated lower overall healthcare expenditures in patients using insulin glargine compared with other types of long- or intermediate-acting insulin.<sup>34</sup> Thus, analysis of hypoglycemia-related insurance claims in several studies supports not only a lower incidence of severe hypoglycemic events but also a lower overall cost with insulin glargine compared with other therapies.

■ **Figure.** Association Between A1C Control and Hypoglycemic Events for Patients on Insulin Glargine vs NPH Insulin\*.<sup>†</sup>



\*The association was predicted with negative binomial regression.

<sup>†</sup>Adapted from *Curr Med Res Opin.* 2005;21:291-298.<sup>32</sup>

A1C indicates glycosylated hemoglobin; NPH, neutral protamine Hagedorn.

## SUMMARY

Intensive insulin therapy is recommended for patients with type 2 diabetes when glycemic goals are not reached with lifestyle modification and oral agents. Hypoglycemia is an expected outcome when aiming to achieve near-normal glycemic control. Despite the low incidence of severe events in patients with type 2 diabetes, hypoglycemia remains a major barrier to insulin therapy. In addition, severe hypoglycemic events result in increased medical expenditures. Prospective clinical studies have established that insulin glargine results in a lower rate of hypo-

glycemia compared with NPH insulin in patients with type 2 diabetes. Meta-analysis also supports the observation that the incidence of severe events is lower with insulin glargine than with NPH insulin. Notably, data from real-world practices and medical claims databases also demonstrate that insulin glargine use is associated with a lower incidence of overall and severe hypoglycemia compared with NPH insulin and other therapies. Finally, medical claims data also are consistent with the clinical trial data and indicate a significantly lower incidence of severe hypoglycemia with insulin glargine, which is accompanied by a reduction in healthcare expenditures. The remarkable consistency of relative hypoglycemia risks for insulin glargine and NPH insulin in prospective clinical trials, observational data from endocrinology clinics, and finally in retrospective managed care database analyses may lend credibility to retrospective database analyses regarding severe hypoglycemia in general.

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### Take-away Points

Although hypoglycemia is a common consequence of achieving tight glycemic control for patients with type 2 diabetes, it need not be a barrier to effective glycemic control.

- Data from real-world practices and medical claims databases demonstrate that insulin glargine use is associated with a lower incidence of overall and severe hypoglycemia compared with neutral protamine Hagedorn insulin and other therapies.
- Medical claims data also indicate a significantly lower incidence of severe hypoglycemia with insulin glargine, which is accompanied by a reduction in healthcare expenditures.

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