EDITORIAL

# Hypoglycemia in Diabetes
## Does Insulin Type Matter?

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**Diabetes care** has made tremendous strides since the discovery of insulin in 1921. Today, patients with diabetes are living longer with fewer complications than previously imagined even 50 years ago. Despite these advances, hypoglycemia remains a significant clinical problem for patients treated with insulin and insulin secretagogues. A recent study[1] of patients with diabetes treated with insulin from 24 countries demonstrated that self-reported hypoglycemia was experienced by more than 80% of patients with type 1 diabetes and nearly half of patients with type 2 diabetes during the course of 1 month.

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Consequences of hypoglycemia range from the mild "inconvenience" of interrupting usual activities for treatment to ramifications as severe as coma, seizures, or death. It is estimated that 10% of the deaths in individuals younger than 40 years with type 1 diabetes are due to hypoglycemia.[2] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[3] which examined the effect of glycemic control on cardiovascular outcomes in older patients with type 2 diabetes, reported that hypoglycemia requiring the assistance of another person was associated with an increased risk of death from any cause, particularly among those randomized to standard glycemic treatment. The concern about hypoglycemia remains a burden shared by patients and their families, and also impedes patients from achieving the glycemic control necessary to reduce the risk of developing the microvascular and potentially macrovascular complications of the disease.

Efforts to reduce the frequency of hypoglycemia have been used since the introduction of insulin for treatment. In the early days, avoiding hypoglycemia meant reducing the insulin dose, often with the consequence of significant hyperglycemia. However, this practice was challenged by the results from the Diabetes Control and Complications Trial (DCCT)[4] and the UK Prospective Diabetes Study (UKPDS),[5] which demonstrated that among patients with type 1 (DCCT) or type 2 (UKPDS) diabetes, microvascular complications can be reduced if the treatment target is near normoglycemia. In these studies, the greatest risk of hypoglycemia was among patients with the lowest hemoglobin $A_{1c}$ values. Currently, it is common practice to manage hypoglycemia by increasing the hemoglobin $A_{1c}$ target and deintensifying the glycemic treatment program. The appropriateness of this approach, however, has recently been challenged. Reports from the type 1 exchange clinic registry[6] and a population of patients with type 2 diabetes[7] demonstrate that patients with a hemoglobin $A_{1c}$ value greater than 9.0% have similar risks for severe hypoglycemia as those with a hemoglobin $A_{1c}$ value of less than 6.0% to 6.5%. Clearly, treatment of hypoglycemia is more complicated than recalibrating the hemoglobin $A_{1c}$ target.

Many approaches have been tried. In the past 15 years, educational and technological approaches have been used to reduce the risk of hypoglycemia in patients with diabetes. Intensive courses in diabetes management, such as the comprehensive Dose Adjusted for Normal Eating (DAFNE) program in the United Kingdom,[8] the use of insulin pumps, and the addition of continuous glucose monitors either uncoupled[9] or coupled[10] with the insulin pump, have demonstrated efficacy in reducing hypoglycemia rates in patients treated with insulin. Insulin also continues to evolve, with the intent of reducing hypoglycemia risk by providing more predictability in onset and duration of action. However, clinicians and their patients have had little opportunity for a head-to-head comparison between the new insulin products, leaving the community with uncertainty about which products will be most successful in achieving desirable glycemic goals while minimizing hypoglycemia.

In this issue of *JAMA*, the publication of the results of the SWITCH 1 trial by Lane and colleagues[11] and the SWITCH 2 trial by Wysham and colleagues[12] offers a rare head-to-head comparison of hypoglycemia rates between 2 commercially available insulin products. Both studies used a randomized, double-blind, treat-to-target, crossover design. Patients with type 1 diabetes (N = 501; SWITCH 1) or patients with type 2 diabetes (N = 721; SWITCH 2) who had 1 or more risk factors for hypoglycemia were enrolled. These patients were randomized to either insulin degludec or insulin glargine U100 for 32 weeks (16-week titration and then 16-week maintenance) and then crossed over to the alternate insulin treatment for an additional 32 weeks (16-week titration and then 16-week maintenance). Both types of insulin are used as the basal component of insulin regimens, but insulin degludec has a longer half-life than insulin glargine U100 (25.4 hours vs 12.1 hours, respectively),[13] a flatter insulin action curve, and less variability.[14]

The aim of both studies was to determine if insulin degludec was associated with a lower rate of hypoglycemia than insulin glargine U100. The primary end point for both studies was the rate of overall severe hypoglycemia (defined as an episode that required the assistance of another person) or symptomatic hypoglycemia during which the blood glucose level was measured and found to be less than 56 mg/dL during the maintenance phase in each treatment period.

In SWITCH 1, the rate of overall symptomatic hypoglycemia (among the 395 patients who completed the trial) was significantly lower with insulin degludec than insulin glargine U100 (2200.9 vs 2462.7 episodes per 100 patient-years of exposure;

rate ratio = 0.89 [95% CI, 0.85-0.94]; $P < .001$).[11] In SWITCH 2, the rates of hypoglycemia (among the 580 patients who completed the trial) were approximately 10-fold less than SWITCH 1, which is expected given the differences between patients with type 2 diabetes and type 1 diabetes.[12] Nevertheless, insulin degludec also was associated with a lower rate of hypoglycemia than insulin glargine U100 (185.6 vs 265.4 episodes per 100 patient-years of exposure; rate ratio = 0.70 [95% CI, 0.61-0.80]; $P < .001$). These observations suggest that regardless of type 1 or type 2 diabetes status, fewer episodes of hypoglycemia occurred during treatment with insulin degludec than insulin glargine U100.

These studies have several strengths. The crossover design allowed each participant to serve as his or her own control. The double-blinded design reduced bias. The analytic plan was well crafted and thorough. Yet, these studies also have several limitations. Each study had a roughly 20% dropout rate, although the data provided suggested that study completers were not substantially different from study dropouts. Another limitation is the definition of hypoglycemia. In these studies, hypoglycemia was only counted when it required the assistance of another person or occurred with symptoms when the blood glucose level was measured to be less than 56 mg/dL. Current guidelines[15] recommend that severe hypoglycemia be defined as an episode regardless of glucose level that requires the assistance of another for treatment and more modest episodes be defined as glucose levels less than 54 mg/dL regardless of symptoms. The rationale is that glucose levels less than 54 mg/dL are associated with impaired cognitive function and predict cardiac arrhythmias and mortality.[15] In addition, repeated episodes with glucose levels less than 54 mg/dL reduce awareness of hypoglycemia and predict severe hypoglycemia.[15] Because the SWITCH 1 and SWITCH 2 studies[11,12] did not count asymptomatic episodes with a glucose value less than 56 mg/dL as hypoglycemia, it will be difficult to compare the SWITCH studies with future trials examining hypoglycemia. The clinical significance of these asymptomatic hypoglycemia episodes remains unknown; however, if they portend impaired awareness of hypoglycemia, interventions will be critically needed. Future trials addressing hypoglycemia may need to include continuous glucose monitoring to establish clinical significance of these asymptomatic hypoglycemia episodes, ultimately with the goal of prevention and treatment.

Do the results of the SWITCH 1 and SWITCH 2 studies[11,12] justify the recommendation of insulin degludec over insulin glargine U100 in patients with type 1 diabetes or type 2 diabetes at risk for hypoglycemia? Both insulin types were comparable with respect to adverse events, weight gain, and glycemic control. Yet, several caveats need to be considered. First, these insulin types were titrated using a set protocol that probably exceeds common clinical practice, so cautious clinicians may want to see the results of a more pragmatic trial. Second, the studies[11,12] were funded by the manufacturer of insulin degludec; however, the study design with randomization and blinding of drug assignment to the study participants and study team helped reduce the risk of bias. Third, these results may not be generalizable to insulin glargine U300 or other alternative basal insulins. Fourth, insurance coverage and affordability are a critical component in the choice of basal insulin.

Despite these concerns, the SWITCH 1 and SWITCH 2 studies[11,12] show that insulin degludec has lower rates of hypoglycemia than insulin glargine U100. Given the risks associated with hypoglycemia and the negative consequences that concerns about hypoglycemia have for patients and their families, any basal insulin associated with a reduced rate of hypoglycemia would seem to represent an advance in therapy.

## ARTICLE INFORMATION

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