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ORIGINAL RESEARCH

Switching from Neutral Protamine Hagedorn (NPH) Insulin to Insulin Glargine 300 U/mL in Older and Younger Patients with Type 2 Diabetes: A Post Hoc Analysis of a Multicenter, Prospective, Observational Study

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ABSTRACT

Introduction: Older age and longer disease duration are key risk factors for hypoglycemia in patients with type 2 diabetes (T2D) who receive insulin. Previous studies have shown that insulin glargine 300 U/mL (Gla-300) improves glycemic control and reduces the risk of hypoglycemia, but whether this effect is observed in older patients switching from neutral protamine Hagedorn (NPH) insulin is unclear.

Methods: In this multicenter, observational study involving patients with T2D aged ≥ 18 years with glycated hemoglobin (HbA_{1c}) ≥ 8%, we compared the safety and effectiveness of switching from NPH insulin to Gla-300 in subgroups of patients differing by age (< 65 vs. ≥ 65 years) and duration of diabetes (≤ 13 vs. > 13 years).

Results: A total of 469 participants were included in the study. From baseline to 6 months after switching to Gla-300, mean HbA_{1c} decreased from 9.23% to 8.13% ($p < 0.001$) among patients aged ≤ 65 years (224 patients), and from 9.15% to 8.20% ($p < 0.001$) among those aged > 65 years (245 patients). The proportion of patients with ≥ 1 episodes of hypoglycemia decreased from 19.1% to 13.6% ($p = 0.11$) among those aged ≤ 65 years, and from 27.6% to 13.0% ($p < 0.001$) among those aged > 65 years; the reduction was significantly greater in those aged > 65 years ($p = 0.001$). The reduction in HbA_{1c} was greater in those with a disease duration ≤ 13 years ($p = 0.007$), but the reduction in hypoglycemia was greater in those with a disease duration > 13 years ($p < 0.0003$).

Conclusion: The switch from NPH insulin to Gla-300 improved glycemic control in older patients with T2D and in those with a longer disease duration. Older patients with T2D and those with a longer disease duration benefited even more from the switch to Gla-300 than younger patients and those with a shorter

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disease duration, with significantly greater reductions in the risk of hypoglycemia.

Keywords: Type 2 diabetes; Elderly; Hypoglycemia; Insulin; NPH; Glargine 300

Key Summary Points

Why carry out this study?

Accumulating evidence shows that insulin glargine 300 U/mL (Gla-300) helps improve glycemic control in patients who do not achieve treatment targets on other insulin formulations and that the use of Gla-300 is also associated with reduced hypoglycemia risk. However, little is known about whether older patients with type 2 diabetes (T2D) and those with longer disease duration also gain benefits from Gla-300 treatment

In this multicenter, observational study among 469 patients with T2D with glycated hemoglobin (HbA_{1c}) $\geq$ 8%, we compared the safety and effectiveness of switching from neutral protamine Hagedorn (NPH) insulin to Gla-300 in subgroups of patients differing by age (<65 . ≥ 65 years) and duration of diabetes (≤ 13 vs. >13 years).

What was learned from this study?

From baseline to 6 months after switching to Gla-300, the mean reductions in HbA_{1c} were similar in both age groups (approx. − 1%), but the reduction in hypoglycemia frequency was much greater in patients aged > 65 years (approx. − 14% of patients) than in those aged $\leq$ 65 years (approx. − 6%). The reduction in HbA_{1c} was greater in those with a disease duration $\leq$ 13 years (− 1.16 vs. − 0.87%), but the reduction in hypoglycemia was greater in those with a disease duration > 13 years (approx. − 14% of patients vs. approx. − 4%).

Older patients with T2D and those with a longer disease duration benefited even more from the switch to Gla-300 than younger patients and those with a shorter disease duration.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.19539268.

INTRODUCTION

Strict glycemic control in type 2 diabetes (T2D) is key to preventing long-term complications but is associated with a substantially increased risk of hypoglycemia [1, 2]. Hypoglycemia can be life-threatening by itself or lead to life-threatening events, such as road traffic accidents, falls, or cardiac arrhythmias. Moreover, fear of hypoglycemia decreases quality of life [3].

Insulin therapy for patients with T2D is associated with a substantially higher risk of hypoglycemia compared with other treatments [4–6]. Older age is a key risk factor for hypoglycemia in patients with T2D who receive insulin, possibly due to cognitive impairment and atypical neurologic symptoms of hypoglycemia in these patients [7, 8]. Polypharmacy, chronic renal or hepatic impairment, and food insufficiency may also increase the risk of hypoglycemia in older patients with T2D [9]. In these patients, hypoglycemia is associated with multidimensional impairment, including a worsening of cognitive function [10, 11].

Reducing the risk of hypoglycemia is crucial in the management of elderly patients with T2D [12, 13] and can be achieved by choosing an adequate insulin formulation. For example, a patient-level meta-analysis of studies among patients aged $\geq$ 65 years showed that the risk of nocturnal hypoglycemia was lower with insulin glargine 300 U/mL (Gla-300) than with insulin glargine 100 U/mL (Gla-100) [14]. In a large, prospective,

observational study, we previously showed that switching from neutral protamine Hagedorn (NPH) insulin to Gla-300 significantly improved glycated hemoglobin (HbA_{1c}) and decreased the risk of hypoglycemia [15]. In this post hoc analysis of data from this earlier study, we investigated whether the effectiveness and safety of switching from NPH insulin to Gla-300 differed between patients aged $\geq$ 65 years and those aged $<$ 65 years. Also, because a long duration of diabetes is a well-recognized risk factor for hypoglycemia [4–7, 16], we additionally compared these outcomes by disease duration ($\geq$ 13 or $<$ 13 years).

METHODS

Study Setting

This observational study was conducted in accordance with the principles laid down in the 1964 Declaration of Helsinki by the 18th World Medical Assembly and its later amendments. The study was approved by the ethics committee of the Jagiellonian University, Krakow, Poland (decision no. 1072.61201.3.2017). All patients provided written informed consent before enrolment.

Participants

Eligible patients had T2D, were aged $\geq$ 18 years, had switched from NPH insulin to Gla-300, and had $HbA_{1c} \geq 8\%$ within 4 weeks prior to enrolment. Previous treatment with NPH insulin should have lasted for $\geq$ 6 months. The following NPH insulin regimens were allowed: basal insulin + oral antidiabetic drugs, basal-bolus insulin (bolus with either regular human insulin or analogs), or human regular premixed insulin containing NPH as the basal component. Detailed inclusion and exclusion criteria have been published previously [15]. Insulin titration was not standardized and was fully at the discretion of the attending physician.

Outcomes

This post-hoc analysis compared the safety and effectiveness of switching from NPH insulin to Gla-300 in subgroups of patients differing by age ($<$ 65 vs. $\geq$ 65 years) and disease duration ($<$ 13 vs. $\geq$ 13 years).The key effectiveness outcome was the value of HbA_{1c}, and the key safety outcome was the proportion of patients with $\geq$ 1 episodes of hypoglycemia in the 4 weeks preceding baseline and in the 6 months after the switch to Gla-300. The remaining endpoints have been published in a previous report [15].

Statistical Analysis

Descriptive statistics were used in accordance with data distribution. Paired *t*-tests were used to compare HbA_{1c} concentrations between patient subgroups differing by age ($\leq$ 65 vs. $>$ 65 years; median age in our sample) or disease duration ($\leq$ 13 vs. $>$ 13 years; median disease duration in our sample). Unpaired *t*-tests were used to compare the change in HbA_{1c} from baseline to 6 months after the switch to Gla-300 between patient subgroups. Paired *t*-tests were used to test the change in HbA_{1c} after the switch within patient subgroups. The McNemar's test was used to compare the change in the proportion of patients with $\geq$ 1 episode of hypoglycemia and the proportion with nocturnal hypoglycemia from baseline to 6 months after the switch to Gla-300 within patient subgroups. A comparison of percentages was used to assess differences between subgroups (Chi-squared statistic). A p value < 0.05 was considered to statistically significant. Statistica software (TIBCO Software Inc., Palo Alto, CA, USA) was used for all calculations.

RESULTS

Of the 499 patients enrolled in the study, 30 patients were not included in the analysis due to discontinued participation due to an unknown cause (n = 19), lost to follow-up (n = 7), switched to another insulin formulation (n = 2), discontinued treatment due to inefficacy (n =

Table 1 Baseline characteristics by age group

Baseline characteristics	Age group	
	Age ≤ 65 years	Age > 65 years
Number of patients, *n* (%)	224 (47.8)	245 (52.2)
Sex, *n* (%)		
Men	124 (55.4)	98 (40.0)
Women	100 (44.6)	147 (60.0)
Age (years)	57.4 ± 6.20	71.6 ± 5.21
Height (cm)	169 ± 9.1	165 ± 9.4
Body weight (kg)	93.6 ± 18.68	88.2 ± 15.75
Body mass index (kg/m^2)	32.6 ± 6.14	32.4 ± 5.21
Waist-to-hip ratio	0.99 ± 0.091	0.99 ± 0.085
Blood pressure (SBP/DBP, mmHg), mean	138/81	140/79
Duration of type 2 diabetes (years)	12.3 ± 6.90	16.3 ± 7.94
Training in diabetes management since diagnosis, *n* (%)		
Individual	147 (65.6)	158 (64.5)
Group	43 (19.2)	39 (15.9)
Self-education	45 (20.1)	66 (26.9)
None	26 (11.6)	31 (12.7)
Individualized diabetes diet, *n* (%)		
Yes	94 (42.0)	85 (34.7)
No	130 (58.0)	160 (65.3)
Regular physical exercise (≥ 30 min, 4 times per week), *n* (%)		
Yes	43 (19.2)	35 (14.3)
No	181 (80.8)	210 (85.7)
SMBG, *n* (%)		
Yes	200 (89.3)	205 (83.7)
No	24 (10.7)	40 (16.3)
Place of residence, *n* (%)		
Voivodeship capital	40 (17.9)	71 (29.0)
Other city	108 (48.2)	105 (42.9)
Village	76 (33.9)	69 (28.2)
Education level, *n* (%)		
University	30 (13.4)	27 (11.0)
High school	148 (66.1)	136 (55.5)
Elementary	46 (20.5)	82 (33.5)
Insulin NPH regimen, *n* (%)		
Basal	78 (34.8)	59 (24.1)
Basal-bolus	142 (63.4)	182 (74.3)
Human regular premixed insulin	4 (1.8)	4 (1.6)
Creatinine (mg/dL)	0.86 ± 0.238	1.03 ± 0.346

Values in table are presented as the mean ± standard deviation unless indicated otherwise

DBP Diastolic blood pressure, *NPH* neutral protamine Hagedorn, *SMBG* self-monitored blood glucose, *SBP* systolic blood pressure

1), and death ($n = 1$). Therefore, 469 participants with 6 months of follow-up were ultimately included in the analysis, of whom 224 were aged ≤ 65 years and 245 were aged > 65 years. The baseline characteristics of the 469 participants included in the analysis are shown in Table 1 according to age group. Of these 469 participants, 217 had a disease duration ≤ 13 years and 252 had a disease duration > 13 years. Details on the characteristics of the cohort have been published previously [15].

From baseline to 6 months after the switch to Gla-300, mean (standard deviation [SD]) HbA_{1c} decreased from 9.23% (1.14) to 8.13% (1.20; $p < 0.0001$) among patients aged

< 65 years, and from 9.15% (1.08) to 8.20% (1.15; $p < 0.001$) among those aged ≥ 65 years. The mean (SD) change in HbA_{1c} did not differ significantly between age groups (− 1.08% [1.19] vs. − 0.94% [1.15]; $p = 0.186$; Fig. 1a).

From baseline to 6 months after the switch to Gla-300, the proportion of patients with ≥ 1 episodes of hypoglycemia decreased from 19.1% ($n = 42$) to 13.6% ($n = 30$; a decrease of − 5.5%; $p = 0.11$) among those aged ≤ 65 years, and from 27.6% ($n = 66$) to 13.0% ($n = 31$, decrease of − 14.6%; $p < 0.0001$) among those aged > 65 years (Fig. 2a). The change in the proportion of patients ≥ 1 episode of hypoglycemia was significantly greater among those aged > 65 years ($p = 0.001$). Among patients > 65 years and ≤ 65 years, the proportion of patients with nocturnal symptomatic hypoglycemia also decreased significantly ($p < 0.001$).

From baseline to 6 months after the switch to Gla-300, mean (SD) HbA_{1c} decreased from 9.20% (1.12) to 8.04% (1.22) among patients with a disease duration of ≤ 13 years, and from 9.18% (1.10) to 8.28% (1.11) among those with a disease duration > 13 years. The mean (SD) change in HbA_{1c} was significantly greater in patients with a disease duration ≤ 13 years than in those with a longer disease duration (− 1.16% [1.21] vs. − 0.87% [1.00]; $p = 0.007$; Fig. 1b).

From baseline to 6 months after the switch to Gla-300, the proportion of patients with ≥ 1 episodes of hypoglycemia decreased from 17.1% ($n = 37$) to 12.7% ($n = 27$; − 4.4%, $p = 0.194$) among those with a disease duration ≤ 13 years, and from 28.2% ($n = 71$) to 13.8% ($n = 34$, − 14.4%, $p < 0.0001$) among those with a disease duration > 13 years. The change in the proportion of patients with one or more episode of hypoglycemia was significantly greater among those with a disease duration > 13 years than in those with a shorter disease duration ($p < 0.0003$, Fig. 2B). The proportion of patients with nocturnal documented hypoglycemia ($p = 0.019$) and nocturnal symptomatic hypoglycemia ($p = 0.023$) decreased significantly in patients with a disease duration > 13 years, but not in patients with a shorter disease duration.

DISCUSSION

In this post hoc analysis of a prospective, observational study among patients with poorly controlled T2D who switched from NPH insulin to Gla-300, the effectiveness of Gla-300 was similar in those aged ≤ 65 years and those aged > 65 years, with comparable reductions in HbA_{1c} after 6 months of treatment. However, HbA_{1c} reductions were lower in those with a disease duration > 13 years than in those with a shorter disease duration. In all subgroups, the improvement in glycemic control was accompanied by a reduced frequency of hypoglycemia. However, the reduction in the frequency of hypoglycemia was substantially greater among older patients (> 65 years) and those with a longer disease duration (> 13 years), such that the subgroup differences in the frequency of hypoglycemia observed at baseline (higher frequency in older patients and those with a longer disease duration) had almost disappeared 6 months after switching to Gla-300.

Before the switch to Gla-300, the mean daily total insulin dose was approximately 60 IU

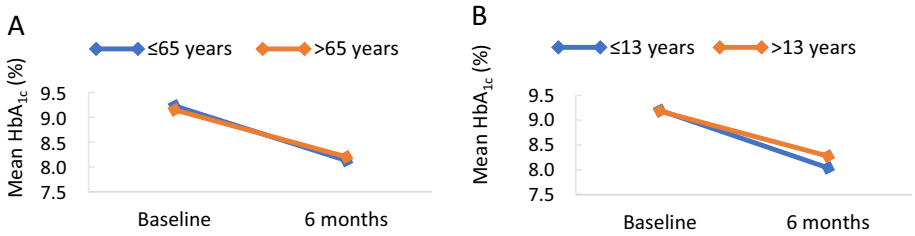

Fig. 1 Mean glycated hemoglobin (HbA_{1c}) values at baseline and 6 months after switching from neutral protamine Hagedorn insulin to insulin glargine 300 U/mL by age group (**a**) and disease duration (**b**)

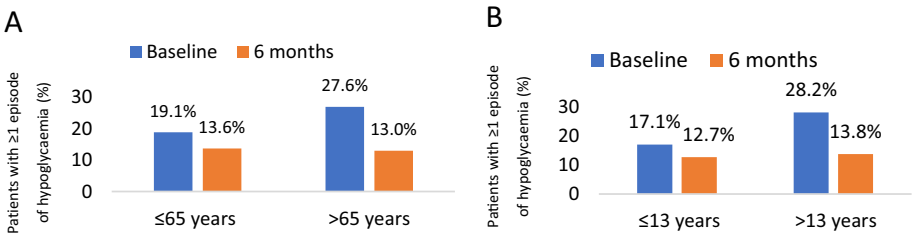

Fig. 2 Percentages of patients with ≥ 1 episodes of hypoglycemia at baseline and 6 months after switching from neutral protamine Hagedorn insulin to insulin glargine 300 U/mL by age group (**a**) and disease duration (**b**). Presented values for the incidence of hypoglycemia represent subgroup data, whereas the reduction in the incidence of hypoglycemia is calculated based on paired values

(NPH insulin, approx. 40 IU, data published in original report [15]). During the study, the total daily insulin dose increased to approximately 70 IU (Gla-300, approx. 30 IU) [15]. Thus, the total dose of insulin increased, but the dose of basal insulin decreased, which might partly explain the simultaneous reductions in HbA_{1c} and hypoglycemia frequency in our sample. Additionally, the decrease in the risk of hypoglycemia in our study might be associated with a reduction in the use of sulfonylureas (approx. 13% of patients at baseline; approx. 9% at the end-of-study), as the use of other antidiabetic medications did not change substantially [15]. The reductions in HbA_{1c} and the risk of hypoglycemia in both age groups could also be due to the trial effect, as patients were likely to be monitored more frequently and had easier access to a diabetes specialist compared with usual care. As there was no placebo arm in our study, we cannot estimate the size of this effect. Despite an increase in the total daily insulin dose during the study, the mean body weight did not change considerably (an increase of < 0.5 kg) [15]

Older patients with T2D who use insulin are at substantial risk of hypoglycemia, which can be life-threatening. A study using blinded continuous glucose monitoring among patients with poorly controlled T2D (HbA_{1c} > 8%) aged ≥ 69 years showed that, within 3 days, 65% experienced ≥ 1 episodes of hypoglycemia (blood glucose < 70 mg/dL), with > 90% of episodes undetected by symptoms or routine self-monitoring of blood glucose [17]. In our study, before switching to Gla-300, the proportion of patients with ≥ 1 episodes of hypoglycemia was much greater among those aged > 65 years than among those aged ≤ 65 years (approx. 27% vs. approx. 19%). The causes of increased risk of hypoglycemia in older patients include atypical symptoms of hypoglycemia, cognitive impairment, and food insufficiency; overtreatment is also an important factor [18]. To reduce the frequency of hypoglycemia, the recommended glycemic targets in older patients with T2D are less strict (HbA_{1c} < 7.5%), particularly in those with serious comorbidities, including cognitive impairment (HbA_{1c} < 8.0–8.5%) [13]. Moreover, de-intensification algorithms, which propose a reduction in insulin dose, have been developed specifically for older patients with T2D to help reduce the risk of hypoglycemia [19].

However, switching to a new-generation basal insulin analog can reduce the frequency of hypoglycemia without compromising, or even necessarily improving, glycemic control. Moreover, accumulating evidence shows that insulin analogs can be used safely in older patients with T2D. In a real-world study of approximately 2000 patients with T2D aged ≥ 65 years, switching from basal insulin to Gla-100/insulin detemir or Gla-300 reduced both HbA_{1c} and the frequency of hypoglycemia [20]. The REALI European Pooled Data Analysis among patients with T2D showed that treatment with Gla-300 improved glycemic control similarly across age groups (< 50 years to > 80 years), and the overall frequency of hypoglycemia was low (approx. 10% of patients with ≥ 1 episodes across all age groups) [21]. In the BRIGHT trial among

insulin-naïve patients with T2D who started either insulin degludec 100 U/mL or Gla-300, improvements in HbA_{1c} and the incidence of hypoglycemia were similar in patients aged < 65 years and those aged > 65 years for both insulin formulations (approx. 70% with ≥ 1 episodes of hypoglycemia) [22]. The LIGHTNING study compared the incidence of hypoglycemia in nearly 200,000 patients with T2D on Gla-300, or first-generation (Gla-100, insulin detemir) or second-generation (insulin degludec) basal-insulin analogs. Rates of severe hypoglycemia among insulin-naïve patients aged ≥ 65 years were lower with Gla-300 than with the other insulin formulations (although differences were only significant vs. insulin detemir and Gla-100) [23]. A patient-level meta-analysis of the EDITION 1, 2, and 3 trials comparing Gla-100 and Gla-300 showed that the benefits of these analogs were similar between patients aged ≥ 65 years and those aged < 65 years, but the risk of nocturnal hypoglycemia was lower with Gla-300 [14]. By showing that Gla-300 improved glycemic control and reduced the frequency of hypoglycemia both in patients aged 65 years and in those aged > 65 years, our study adds to the existing evidence supporting the use of Gla-300 in older patients with poorly controlled T2D, particularly because the reduction in the frequency of hypoglycemia in our study was greater among patients aged > 65 years.

The risk of hypoglycemia in patients with T2D uncontrolled on different insulin regimens decreased substantially after switching to Gla-300 in previous real-world studies [24, 25]. In our study, the reduction in hypoglycemia risk was greater in patients aged > 65 years primarily because these patients had substantially greater hypoglycemia frequency at baseline. In principle, hypoglycemia results from inadequate insulin treatment, with older patients having less effective counterregulatory mechanisms. Therefore, although optimizing insulin treatment helps avoid hypoglycemia in all patients, the benefits might be the greatest among those with less effective counterregulatory mechanisms, including older patients.

In addition to old age, long disease duration is an important risk factor for hypoglycemia among patients with T2D, which is due—among others things—to an impaired counter-regulatory response to hypoglycemia [5, 26]. We found that the switch from NPH insulin to Gla-300 reduced the frequency of hypoglycemia in patients with long-lasting diabetes, although these patients had a lower reduction in HbA_{1c} than did those with a shorter disease duration. A meta-analysis of four studies comparing insulin glargine and NPH insulin among patients with T2D showed that the risk of nocturnal hypoglycemia correlated positively with disease duration among those receiving NPH but not among those receiving insulin glargine [27]. Patients with a long disease duration therefore seem to benefit particularly from Gla-300 (vs. NPH insulin).

CONCLUSIONS

The results of our study indicate that patients aged > 65 years benefit even more from switching from NPH insulin to Gla-300 than do those aged ≤ 65 years, with a similar reduction in HbA_{1c} but a greater reduction in the frequency of hypoglycemia. Similarly, the reduction in the frequency of hypoglycemia was higher in patients with a longer duration of T2D (≥ 13 years), but the reduction in HbA_{1c} was smaller than in those with a shorter disease duration.

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Data Availability. The data supporting conclusions of the study can be accessed on request. To request for data, the readers should contact the corresponding author (T Klupa) directly. Qualified researchers may request access to patient-level data and related documents (including, for example, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of the trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

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