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A prospective evaluation of the effectiveness and safety of insulin glargine 100 U/mL (Gla-100) in adults with diabetes mellitus in Poland. The LARE observational study

ABSTRACT

Introduction. Insulin glargine 100 U/ml (Gla-100) is a long-lasting basal insulin analog injected once daily. This real-life study aimed to evaluate the efficacy and safety of Gla-100 in patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM), who were recently switched from isophane (NPH) insulin.

Methods. This multicenter, prospective, 52-week observational study included 321 patients with T1DM and 766 with T2DM. The primary endpoint was the percentage of participants with a HbA1c reduction of ≥ 0.5% at 52 weeks. The secondary endpoints included fasting plasma glucose (FPG) and HbA_{1c} reduction over time, and hypoglycemic events.

Results. Of the 1,087 patients included, 69.9% achieved the primary endpoint, while the mean HbA_{1c} decreased by 1.03% and the mean FPG by 31.8 mg/dL at 52 weeks. The average annual rate of severe hypoglycemia was 0.017 events per patient-year and 0.82 events per patient-year for nocturnal hypoglycemia. The proportion of participants experiencing severe diurnal or nocturnal hypoglycemia was significantly lower in the four weeks prior to the study end than the four weeks before the switch from NPH insulin ($p < 0.0001$ for diurnal hypoglycemia in T1DM and < 0.002 for diurnal hypoglycemia in T2DM; $p < 0.0001$ for nocturnal hypoglycemia in both T1DM and T2DM). Body weight did not change substantially throughout the study (mean increase of 0.3 kg for T1DM and 0.1 kg for T2DM).

Conclusions. Patients with T1DM or T2DM in whom diabetes was not well controlled with NPH insulin treatment achieved better glycemic control at a lower risk of hypoglycemia after switching to Gla-100 in routine clinical practice. (Clin Diabetol 2021; 10; 2: 169–179)

Key words: insulin, Lantus, glargine, NPH, type 1 diabetes, type 2 diabetes

Introduction

Insulin glargine 100 U/ml (Gla-100), the first basal insulin analog injected once-daily with long-lasting efficacy, can be used in combination with prandial insulin preparations and non-insulin antidiabetic agents according to individual patient needs [1]. Gla-100 helps provide individualized therapy, which is the cornerstone of effective glycemic control defined by the Polish Diabetology Association as $HbA_{1c} \leq 6.5\%$ for type 1 diabetes mellitus (T1DM) and early type 2 diabetes mellitus (T2DM) [2].

Currently, a large proportion of patients with diabetes in Poland do not achieve satisfactory glycemic control, with the average HbA_{1c} values of 8.98% in patients with T1DM and 8.03% in those with T2DM [2]. Real-life studies show that most patients with diabetes do not achieve target HbA_{1c} values despite lifestyle and pharmacologic interventions, with HbA1c values > 7.5% occurring in 45% of patients and >8.0% in 37%

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[3, 4]. In the US, the proportion of patients with HbA_{1c} > 9.0% ranges between 29% and 48% [5].

Economic issues are an obstacle to intensive diabetes control; for example, insulin glargine is about twice as expensive as isophane (NPH) insulin [6]. A retrospective analysis of medical records of American patients with T2DM revealed that better glycemic control was associated with older age, type of medical insurance, higher income, and comorbid diseases, whereas the use of prandial or pre-mix insulin was significantly associated with higher HbA_{1c} levels [7]. In Poland, long-acting insulin analogs only became reimbursed in 2013, with most patients using regimens based on NPH insulin, which was introduced over 50 years earlier. However, since long-acting insulin analogs have been reimbursed in patients with T1DM and some patients with T2DM, their use has become more frequent.

In Poland, long-acting insulin analogs are currently reimbursed in patients with T1DM and in those with T2DM who have received NPH insulin for 6 months or longer and have HbA_{1c} values ≥ 8% or who experience recurrent severe or nocturnal hypoglycemia. Large studies have shown that insulin glargine effectively lowers HbA1c without increasing hypoglycemia risk in patients receiving oral antidiabetic drugs [8] or who switch from NPH insulin [9]. However, to date, there are no data confirming the efficacy and safety of Gla-100 (Lantus®) among patients in Poland who have switched from NPH insulin.

Therefore, the primary aim of this study was to evaluate the efficacy (HbA1c reduction) among patients using Gla-100 in a real-life setting in Poland. Moreover, we assessed other efficacy and safety endpoints, including the risk of hypoglycemia.

Methods

Patients

The inclusion criteria were as follows: adult patients (≥ 18 years) with T1DM or T2DM who were switched from NPH insulin (any dosage regimen) to Gla-100 during the four weeks prior to enrollment due to unsatisfactory diabetes control (HbA_{1c} ≥ 7.5% in T1DM and ≥ 8 % in T2DM), and for whom data on HbA_{1c}, FPG, and insulin dose (during the four weeks prior to the switch) were available. The exclusion criteria were as follows: participation in any other clinical trial within the last three months, pregnancy, hypersensitivity to glargine, or drug/alcohol addiction within the last two years.

Of 729 diabetes outpatient clinics and 34 hospital wards, we had to recruit 110 sites to cover at least 15% of these medical centers. Among the doctors who completed a feasibility questionnaire, we randomly selected 112 from 112 centers (complete list in Appendix 1). Each center enrolled the first consecutive 5–15 eligible patients. The sample size, estimated on the basis of the size of the population aged ≥ 18 years (31,500,000) in Poland and the incidence of T1DM and T2DM in this population (9%), with 95% confidence interval (CI) and 1.5% error, was 963 patients. With a 10% margin on data gaps, the final sample size required for our study was 1,060 patients.

Local Ethics Committees approved the study at all individual sites (Appendix 1), and all patients provided written informed consent before enrollment. The study was conducted in compliance with all international guidelines and national laws, including the Declaration of Helsinki, as amended.

Data collection

Data were collected between 12 April 2014 and 04 February 2016 from medical records that contained previous medical history and ancillary tests before the switch from NPH insulin to Gla-100 (three months before the switch). After enrolment, data were gathered during a 12-month follow-up. During visit 1, the inclusion and exclusion criteria were verified. Eligible patients were informed in detail about the study and were asked to sign a consent form to participate. During the same visit, the following information was gathered: demographic data; concomitant diseases; diabetes complications (micro- and macroangiopathy); and previously used antidiabetic medications, including an insulin algorithm and the daily dose of basal and prandial insulin, and oral antidiabetic drugs (in patients with T2DM), before and after the switch from NPH insulin to insulin glargine. We also gathered data on glycemic control (HbA_{1c}, blood glucose at fasting and two hours after a meal, glucose profile from self-monitoring), hypoglycemia, and glycemic profiles while on NPH insulin. The following data were collected if available: serum creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, albumin in urine, and micro-/macroalbuminuria. Based on these data, the physician modified the treatment using their clinical judgment, including the type or dose of basal or short-acting insulins and other medications.

During visits 2 and 3, the following data were gathered: body weight, waist/abdomen circumference, blood pressure, HbA_{1c} (if measured), blood glucose at fasting and two hours after a meal, blood glucose profile from self-monitoring for the period after the previous visit, diurnal and nocturnal episodes of hypoglycemia since the last visit, daily insulin doses,

and time and number of insulin injections per day. In patients with T2DM, the use of oral antidiabetic drugs was recorded.

The frequency of hypoglycemia was assessed for the 4-week period before the switch to Gla-100, and at visit 2 and visit 3. We obtained the most recent data on self-measured glucose profiles before the switch to Gla-100 and before visit 2 and visit 3.

Study endpoints

The primary endpoint was the percentage of patients who achieved a ≥ 0.5% HbA1c reduction at 52 weeks. The secondary endpoints included the mean HbA_{1c} value and its change from baseline; the mean FPG value and its change from the baseline; the number of severe hypoglycemia events; the number of nocturnal hypoglycemia events (events during sleep); and the number of mild or moderate hypoglycemia events.

Severe hypoglycemia was defined according to the American Diabetes Association and the Endocrine Society as glycemia of < 70 mg/dL with symptoms requiring an assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions [10]. Non-severe hypoglycemia was defined as hypoglycemia that did not require the assistance of another person. Non-severe hypoglycemia was regarded as moderate (hypoglycemia symptoms interfering with daily life) or mild (hypoglycemia symptoms not interfering with daily life). Nocturnal hypoglycemia was defined as an episode of hypoglycemia during sleep.

Statistical analysis

Only patients with complete data from the three visits were included in the statistical analysis. The results are presented by diabetes type. For categorical and ordinal variables, percentages were calculated. Parametric variables are presented as means, standard deviations (SD), and range. The chi-squared test was used to compare hypoglycemia frequency between visits. A p-value of < 0.05 was considered statistically significant. The safety analysis covered the period from patient enrollment (visit 1) to study end (visit 3). Safety was summarized as the number of hypoglycemic events reported by the patients (considering the severity and time of occurrence) and the number of adverse events (AE) and serious adverse events (SAE) as classified by the System Organ Classification, taking into account the severity, course, association with insulin glargine, and outcome.

Results

Patient characteristics

Overall, 1,100 patients were enrolled in the study. Data were available for all three visits for 1,087 patients (98.8%); 13 patients were excluded from further analysis due to the lack of data from visits 2 and 3.

Of the 1,087 patients included, 321 had T1DM (29.5%) and 766 (70.5%) had T2DM. Insulin use for six months or longer was found in 89.3% of patients with T1DM and 93.0% of patients with T2DM. Multiple daily injections (≥ 4 injections per day) were used by 87.4% of patients with T1DM and 63.3% of patients with T2DM. Table 1 shows the remaining baseline characteristics of patients.

Insulin dose and body weight

In total, 1,042 (94.7%) patients stayed on Gla-100 at the end of the study. The mean dose of Gla-100 increased numerically throughout the study among patients with T1DM and T2DM (Figure 1A). Similarly, the mean dose of prandial insulin increased numerically among patients with both types of diabetes (Fig. 1B). The mean body weight remained stable throughout the study among patients with T1DM (visit 1, 77.0 ± 14.3 kg; visit 2, 77.2 ± 14.0 kg; visit 3, 77.2 ± 13.9 kg) and T2DM (visit 1, 90.2 ± 17.9 kg; visit 2, 90.1 ± 17.9 kg; visit 3, 90.3 ± 18.0 kg).

Efficacy

The primary endpoint (i.e., a ≥ 0.5% HbA_{1c} reduction by at 52 weeks) was achieved by 69.9% of patients in the overall population (and by 70.1% of patients with T1DM and 69.8% of patients with T2DM). HbA_{1c} values decreased by 1.03% in the overall population (by 1.01% among patients with T1DM and 1.04% in those with T2DM; Figure 2A). In the overall population, HbA_{1c} values > 7% were found in 99.4% of patients at baseline, and in 82.1% at the study end (99.1% *vs* 73.7% in T1DM, 99.5% *vs* 85.8% in T2DM).

FPG decreased by 31.8 mg/dL in the overall population, and by 31.1 mg/dL in the T1DM subgroup and 32.4 mg/dL in the T2DM subgroup (Figure 2B). Glycemia values from self-measurement decreased from visit 1 to visit 2, but remained stable at visit 3, in both the T1DM and T2DM subgroups (Figure 3).

Safety

There were a total of 61 AE. Fifteen AEs, including nine classified as serious adverse events (SAE), occurred in 12 (3.2%) patients with T1DM. In the T2DM subgroup, 31 patients (4.0%) experienced 46 AE, of which 19 (41.3%) were classified as serious. The numbers of AE (SAE) in patients with T1DM *vs* T2DM were as follows: circulatory, 2 (2) *vs* 7 (7); respiratory, 3 (1) *vs* 9 (2); central nervous system, 2 (2) *vs* 3 (2); gastrointestinal, 0 (0) *vs* 7 (5); endocrine or diabetic 5 (4) *vs* 4 (1); genitourinary, 0 (0) *vs* 4 (1); musculoskeletal, 2 (0) *vs* 6 (1); and other, 1 (0) *vs* 6 (0).

Table 1. Baseline characteristics of study cohort

	Type 1 diabetes mellitus (n=321)	Type 2 diabetes mellitus (n=766)
Women, n [%]	137 ± 42.7	382 ± 49.9
Age [years], mean ± SD	45.8 ± 13.02	62.1 ± 9.56
Duration of diabetes [years], mean ± SD	15.9 ± 11.3	13.3 ± 7.4
HbA^{1c} [%], mean ± SD	8.8 ± 1.22	9.1 ± 1.13
FPG [mg/dl], mean ± SD	161.5 ± 57.1	170.3 ± 48.8
Last daily NPH dose [IU], mean ± SD	22.7 ± 10.4	26.0 ± 19.9
Last daily NPH dose [IU/kg], mean ± SD	0.29 ± 0.14	0.28 ± 0.22
Prandial insulin dose before switch [IU]*, mean ± SD	32.2 ± 15.5	41.0 ± 19.6
Prandial insulin dose before switch [IU/kg]*, mean ± SD	0.42 ± 0.20	0.45 ± 0.22
Body weight [kg], mean ± SD	77.0 ± 14.3	90.2 ± 17.9
BMI [kg/m^2], mean ± SD	26.2 ± 3.96	31.9 ± 5.58
Comorbidities, n [%]		
Retinopathy	110 (34.3)	236 (30.8)
Nephropathy	29 (9.0)	98 (12.8)
Neuropathy	84 (26.2)	192 (25.3)
Cardiomyopathy	6 (1.9)	60 (7.8)
Coronary heart disease	24 (7.5)	298 (38.9)
Stroke	4 (1.2)	40 (5.2)
Diabetic foot	10 (3.1)	38 (5.0)
Arterial hypertension	135 (42.1)	624 (83.8)
Hypercholesterolemia	100 (31.2)	397 (51.8)
Oral antidiabetic drugs, n [%]		
Metformin	—	532 (95.9)
Sulphonylurea		105 (18.9)
Alpha glucosidase inhibitors		27 (4.9)
Dipeptidyl peptidase-4 inhibitors		6 (1.1)
Glitazones		1 (0.2)

*if used; BMI — body mass index; FPG — fasting plasma glucose; IU — international units; NPH — isophane insulin — SD, standard deviation

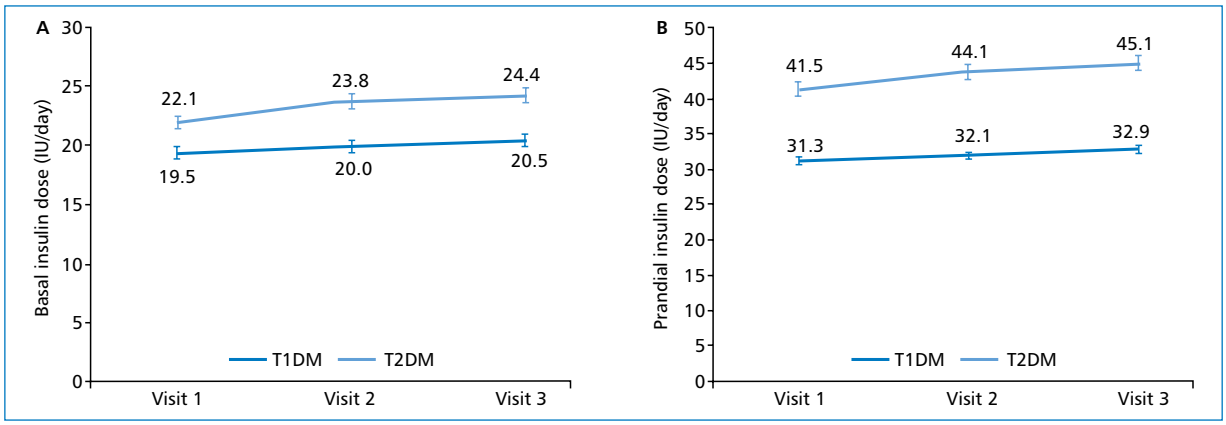

Figure 1. Daily doses of basal (**A**) and prandial insulin (**B**) throughout the study (means ± standard errors of the mean). T1DM — type 1 diabetes mellitus; T2DM — type 2 diabetes mellitus

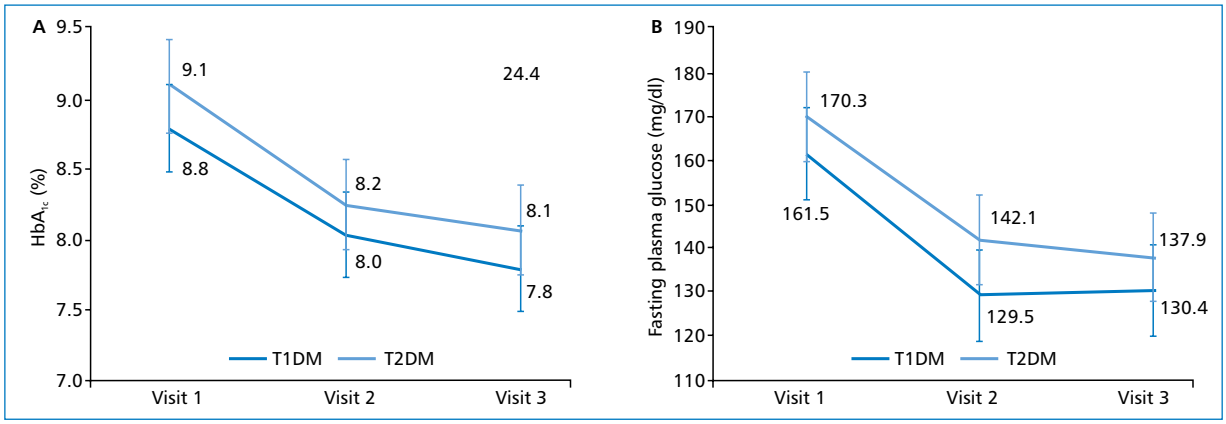

Figure 2. Values of HbA_{1c} (**A**) and fasting plasma glucose (**B**) throughout the study (means ± standard errors of the mean). T1DM — type 1 diabetes mellitus; T2DM — type 2 diabetes mellitus)

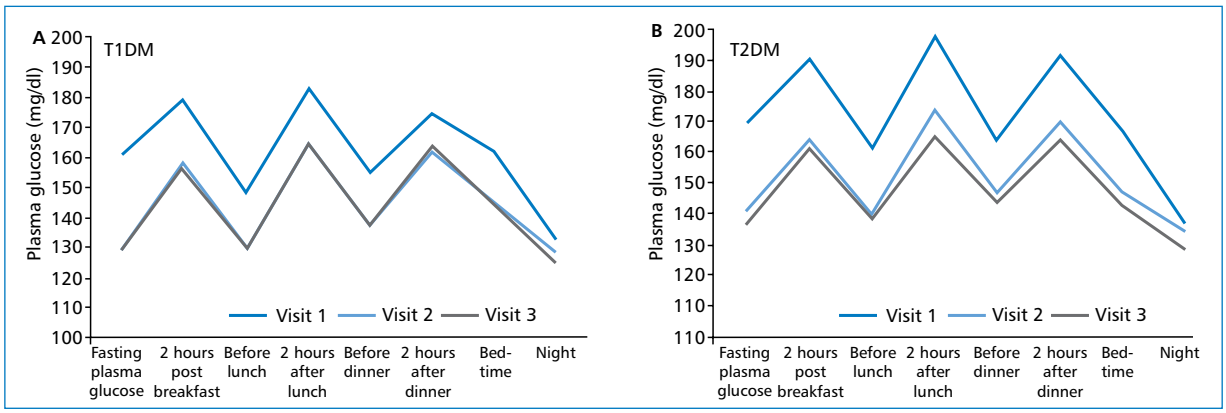

Figure 3. Self-measurement glucose profiles (mean values) throughout the study in patients with type 1 (**A**) and type 2 diabetes mellitus (**B**).

Table 2. Number and incidence proportion of participants experiencing mild, moderate, and severe hypoglycemia, diurnal and nocturnal, during the 4-week period before baseline, visit 2, and visit 3

	Type 1 diabetes mellitus (n = 321)			Type 2 diabetes mellitus (n = 766)		
	Baseline (n = 321)	Visit 2 (n = 317)	Visit 3 (n = 316)	Baseline (n = 766)	Visit 2 (n = 742)	Visit 3 (n = 756)
Diurnal, n [%]						
Mild	144 (44.9)	160 (50.5)	165 (52.2)	229 (29.9)	243 (32.7)	265 (35.1) p < 0.03
Moderate	80 (24.9)	61 (19.2)	58 (18.4) p < 0.044	103 (13.4)	69 (9.3) p < 0.01	80 (10.6)
Severe	20 (6.3)	4 (1.3) p < 0.001	3 (0.9) p < 0.001	17 (2.2)	2 (0.3) p < 0.001	3 (0.4) p < 0.002
Nocturnal, n [%]						
Mild	98 (30.5)	72 (22.7) p < 0.026	85 (26.9)	179 (23.4)	97 (13.) p < 0.001	113 (14.9) p < 0.001
Moderate	58 (18.1)	14 (4.4) p < 0.001	17 (5.4) p < 0.001	109 (14.2)	25 (3.4) p < 0.001	26 (3.4) p < 0.001
Severe	18 (5.6)	0 p < 0.001	4 (1.3) p < 0.003	30 (3.9)	1 (0.1) p < 0.001	0 p < 0.001

All p-values are for comparisons with baseline (Chi-squared tests)

The number and incidence proportion of participants with severe or moderate diurnal or nocturnal hypoglycemia during the four weeks before visit 2 and visit 3 were significantly lower in the T1DM and T2DM subgroups than the 4-week period before baseline, i.e., on NPH insulin (Table 2).

The average number of severe hypoglycemia episodes per patient-year during Gla-100 treatment was 0.017 in the overall study population, 0.032 in the T1DM subgroup, and 0.011 in the T2DM subgroup. The average number of nocturnal hypoglycemia episodes per patient-year during Gla-100 treatment was 0.82 in the overall population, 1.29 in the T1DM subgroup, and 0.62 in the T2DM subgroup.

Discussion

This real-life study showed that Gla-100 treatment improved glycemic control and decreased hypoglycemia risk among patients with T1DM or T2DM who did not achieve satisfactory glycemic control during NPH insulin treatment. The mean doses of Gla-100 and prandial insulin increased during the study, but body weight remained stable.

Although over 40 therapeutic schemes have been approved for patients with T2DM over the past 13 years, only 30–50% of them help to achieve HbA_{1c} < 7.0% [3]. Carls et al. analyzed why treatment efficacy in diabetes differs between clinical trials and real-world studies; they concluded that poor medication adherence was an important reason [11]. In our study, the primary endpoint (HbA1c reduction of ≥ 0.5%) was reached by nearly 70% of patients, but over 80% did not achieve HbA_{1c} ≤ 7% at the study end. Similarly, most patients did not reach the recommended FPG levels at the study end. This suboptimal efficacy could be due to low insulin doses resulting from insufficient titration (i.e., mean Gla-100 dose increase of 1.0 IU in T1DM and 2.3 IU in T2DM at week 26; mean prandial insulin dose increase of 1.6 IU in T1DM and 3.6 IU in T2DM). The insufficient Gla-100 titration in our study could be due to rare clinic visits, unsatisfactory awareness of diabetic issues, fear of weight gain or hypoglycemia, and insufficient adherence to treatment or self-monitoring of blood glucose. The insufficient titration of prandial insulin in our study suggests that patients rarely checked their glycemia or responded inadequately to their glycemia values.

Despite the suboptimal glycemic control in our study, a previous study showed patients with T2DM aged ≥ 60 years could achieve benefits (lower mortality rate) at HbA_{1c} values < 8.0%, whereas intensive insulin therapy (HbA_{1c} < 6.0%) could increase the risk of death [12]. In contrast, another study found that the risk of hypoglycemia requiring medical assistance increased with each 1% increment in the average HbA_{1c} concentration [13]. Therefore, perhaps the ideal HbA_{1c} target should be assessed on an individual basis.

The improvement of HbA_{1c} and FPG and stable body weight during Gla-100 treatment in our study is in line with previous observational studies conducted among patients with poorly-controlled T2DM, such as the EARLY [14], RESOLUTE [15], PARTNER [16], and ESPRIT [17] studies. Similar changes in HbA1c and FPG values were also observed in the LADI study [18] among patients with T1DM, although only one-third of participants in that study switched from NPH insulin. Interestingly, the TOP observational study [19] of patients with T2DM reported greater improvements in HbA1c (-1.4%) and FPG (-59 mg/dL) over 12 months than those seen in our study, while the mean daily dose of insulin glargine (22.8 IU) at 12 months was lower than in our study. This may have been due to differences in the treatment algorithms applied in Germany compared to Poland.

In addition to improved glycemic control, we confirmed Gla-100 treatment significantly lowered the risk of severe or moderate hypoglycemia compared to NPH insulin. Hypoglycemia can be fatal and can also increase the risk of other adverse events or be a marker of vulnerability to serious adverse events. Indeed, in a 5-year follow-up study among 11,000 patients with T2DM, severe hypoglycemia was found to be strongly associated with increased risks of major macrovascular events (~3-fold increase), major microvascular events (~2-fold increase), death due to a cardiovascular cause (~3-fold increase), and death from any cause (~3-fold increase) [20]. We found the frequency of hypoglycemia episodes decreased during Gla-100 treatment. This observation is likely because the hypoglycemic effect of insulin glargine is less variable than that of NPH insulin [21].

We also found hypoglycemia was more frequent in T1DM than T2DM. Our findings are in line with a meta-analysis in which the frequency of symptomatic, overall, and nocturnal hypoglycemia was significantly lower in patients with T2DM treated with either insulin glargine or detemir compared to NPH insulin [22]. A systematic review of 116 randomized clinical trials concluded that long-acting insulin analogs, when used in combination with oral medications, are associated with similar glycemic control but fewer hypoglycemic episodes compared to NPH insulin [23]. This conclusion was later confirmed in another review, which also indicated that suboptimal glycemic control was common in clinical trials [24]. Moreover, Monami et al. reported that long-acting insulin analogs did not improve glycemic control compared to NPH in T2DM, but they did reduce the risk of nocturnal and symptomatic hypoglycemia [25]. Similar results were observed in Asian patients with T2DM [26]. In contrast, a reduced risk of hypoglycemia, as well as improved glycemic control, while on insulin glargine were reported in the

AT.LANTUS study, a 24-week, multinational, multicenter randomized trial investigating glycemic control and safety in 686 patients who switched from premix to glargine [27]. Moreover, similar findings were also reported by a meta-analysis involving 698 patients from Adriatic countries [28]. Likewise, we found a reduced risk of hypoglycemia, in addition to improved glycemic control after switching from NPH insulin to Gla-100 in patients with T1DM and T2DM in this study.

Unlike dietary changes and most oral diabetic medications, insulin use can cause weight gain [29]. However, body weight remained stable among the patients included in our study. This observation may have been due to the low insulin doses used, but may also support the advantage of insulin glargine over NPH insulin. Indeed, similar results were described by Holman et al., who reported similar HbA1c values as in our study, but even less weight gain among patients with T2DM who switched from metformin or sulfonylurea to basal or biphasic insulin compared to those who switched to prandial insulin [30]. Furthermore, another study among patients with inadequately-controlled T2DM revealed an insulin glargine dose of 27.7 IU decreased HbA1c (from 8.9% to 7.3%) without any observed weight gain [31]. Therefore, insulin glargine appears to have advantages over NPH insulin in terms of maintaining body weight.

There are also reports that treatment satisfaction with insulin glargine is greater than with NPH insulin. For example, in one study, over 90% of physicians and over 95% of patients were satisfied or highly satisfied with insulin glargine treatment [31]. Improved treatment satisfaction with insulin glargine (in addition to improved glycemic control and low hypoglycemia risk) was also reported in an observational, real-life study evaluating the efficacy and safety of insulin glargine plus oral antidiabetic drugs in patients with T2DM previously treated with premixed insulin [32]. The overall improvement in treatment satisfaction could be due to a lower frequency of nocturnal hypoglycemia, decreased need to take time off work, or fewer activities hampered by diabetes [33].

Our study had limitations. First, the study was observational. However, real-life observational studies are important to evaluate the efficacy and safety among heterogeneous groups of patients with complex, chronic diseases [34]. Second, our study was not controlled. The multicenter, randomized controlled trial GRADE should give more information on the safety and efficacy of insulin glargine [35]; the results are expected in July 2021 [36].

Conclusions

In summary, switching from NPH insulin to Gla-100 is an effective and safe way to improve diabetes control in patients with T1DM and T2DM. Most patients experienced an improvement in diabetes control with a significantly lower risk of diurnal and nocturnal hypoglycemia and almost no weight gain. A low basal insulin dose and poor titration resulted in FPG values above the recommended targets. This study showed that the reimbursement of glargine in Poland as a second-line treatment of T2DM is justified.

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Contribution statement

GD developed the concept for the study and contributed to the design of the research. Both authors were involved in data collection and data analysis. Both authors edited and approved the final version of the manuscript.

Conflict of interest statement

This study was sponsored by Sanofi–Aventis, Poland. The sponsor had no role in assigning treatments, dose decisions or patient identification during the study. Grzegorz Dzida and Tomasz Szczepanik received remuneration/fees for activities on behalf of Sanofi, Novo Nordisk, Astra Zeneca.

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