A randomized trial comparing the rate of hypoglycemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study)

Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). Pediatric Diabetes 2013: 14: 593–601.

Background: Avoidance of hypoglycemia is a key consideration in treating young children with type 1 diabetes (T1DM).

Key Objective: To evaluate hypoglycemia with insulin glargine vs. neutral protamine Hagedorn (NPH) insulin in young children, using continuous glucose monitoring (CGM).

Subjects: Children of 1 to <6 yr treated with once-daily glargine vs. once- or twice-daily NPH, with bolus insulin lispro/regular human insulin provided to all.

Methods: Twenty-four week, multicenter, randomized, open-label study. Primary endpoint was event rate of composite hypoglycemia [symptomatic hypoglycemia, low CGM excursions (<3.9 mmol/L) or low fingerstick blood glucose (FSBG; <3.9 mmol/L)]. Noninferiority of glargine vs. NPH was assessed for the primary endpoint.

Results: One hundred and twenty-five patients (mean age, 4.2 yr) were randomized to treatment (glargine, n = 61; NPH, n = 64). At baseline, mean HbA1c was 8.0 and 8.2% with glargine and NPH, respectively. Composite hypoglycemia episodes/100 patient-yr was 1.93 for glargine and 1.69 for NPH; glargine noninferiority was not met. Events/100 patient-yr of symptomatic hypoglycemia were 0.26 for glargine vs. 0.33 for NPH; low CGM excursions 0.75 vs. 0.72; and low FSBG 1.93 vs.1.68. There was a slight difference in between-group severe/nocturnal/severe nocturnal hypoglycemia and glycemic control. All glargine-treated patients received once-daily injections; on most study days NPH-treated patients received twice-daily injections.

Conclusions: While glargine noninferiority was not achieved, in young children with T1DM, there was a slight difference in hypoglycemia outcomes and glycemic control between glargine and NPH. Once-daily glargine may therefore be a feasible alternative basal insulin in young populations, in whom administering injections can be problematic.
Increases in the prevalence of type 1 diabetes mellitus (T1DM) among those <18 yr of age have been reported in Europe (1, 2), the USA (3, 4), and elsewhere (5). In particular, a doubling of newly diagnosed cases in children <5 yr of age is expected by 2020 in Europe (1). In young children ≤6 yr of age, the management of T1DM is a challenge, as the rate of treatment-related hypoglycemia in this cohort is more than twofold higher than that observed among older children (6, 7). This may be partly due to increased physical activity and irregular dietary patterns that have been identified as risk factors for hypoglycemia in children and adolescents with T1DM (6).

While the health risk of long-term hyperglycemia is much greater than any lasting consequences of hypoglycemia, the fear of hypoglycemia is stressful for parents of children with T1DM (8). Young children neither tolerate hypoglycemia well – seizures (6, 9), cognitive impairment (10), and structural neurologic abnormalities are not uncommon (11) – nor do they verbalize the symptoms well. Moreover, almost 60% of young children experience impaired awareness of hypoglycemia, which is associated with a 1.6-fold increased risk of severe hypoglycemia (9). Consequently, avoidance of hypoglycemia – particularly severe hypoglycemia – is a key consideration in the treatment of young children with T1DM.

Continuous glucose monitoring (CGM) may be useful in detecting episodes of potential or actual hypoglycemia. The PRESCHOOL study used CGM to assess the occurrence of hypoglycemia in children <6 yr of age with T1DM receiving insulin lispro or regular human insulin at mealtimes, plus one of two basal insulins: once-daily prebreakfast insulin glargine or once- or twice-daily neutral protamine Hagedorn (NPH) insulin. Insulin glargine is a once-daily basal insulin with a flat plasma pharmacokinetic profile that has shown greater blood glucose stability, lower fasting glucose, and a lower risk of hypoglycemia, especially nocturnal hypoglycemia, in adult patients with T1DM compared with basal insulins with pharmacokinetic peaks (12). Retrospective data have also shown that insulin glargine reduced the risk of severe hypoglycemia (especially nocturnal) compared with NPH insulin in 128 children with T1DM aged <6 yr (13). Prospective data of this kind in large groups of young children with T1DM, however, are lacking. Therefore, as adult data are not directly transferable to pediatric patients (14), PRESCHOOL aimed to address this knowledge gap.

**Methods**

**Subjects and study design**

PRESCHOOL was a 24-wk, multicenter (n = 61), multinational (n = 16), randomized, open-label, parallel-group study. Children aged ≥1 to <6 yr with T1DM (≥1 yr duration) who were receiving multiple daily insulin injections for ≥2 months were included if they had glycated hemoglobin (HbA1c) values at screening of 6–12% (inclusive), and provided a family member was able to generate 6 days’ worth of CGM data during the 2-wk run-in period. Subjects using anti-hyperglycemia agents other than insulin were excluded.

Patients were centrally randomized in a 1:1 ratio to one of the two treatment groups. Randomization was stratified based on the number of hypoglycemic events (<0.5 vs. ≥0.5 episodes/24 h) and baseline HbA1c (<8.5% vs. ≥8.5%) during screening; stratification was expected to contribute to clearer conclusions regarding the respective efficacy variables and overall efficacy of insulin glargine.

Patients were randomized to treatment with either morning insulin glargine or once- or twice-daily NPH; all received bolus insulin lispro or regular human insulin (at mealtime and/or bedtime). Insulin was titrated to achieve fasting blood glucose of 5–8.0 mmol/L, bedtime blood glucose of 6.7–10.0 mmol/L, and nocturnal blood glucose of 4.4–9.0 mmol/L. Best efforts were made to complete the up-titration of both basal insulins by week 12. Doses of insulin glargine and NPH insulin were increased no more often than once a week, but doses could be reduced due to hypoglycemia at any time.

The 24-wk treatment period was preceded by a 2-wk run-in period and followed by a 2-wk post-treatment period. Clinic visits occurred at screening (week −3/−2), randomization (week 0), weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 (end of treatment), and 26 (follow-up). CGM data were captured at weeks 0, 2, 4, 8, 12, 16, 20, and 24 using the DexCom Seven Plus CGM system (DexCom, San Diego, CA, USA). Patients were required to use CGM for ≥6 total days for ≥6 occasions during the on-treatment period, of which two occasions had to occur after week 14. Over each CGM occasion, at least 1296 usable CGM glucose values were to be recorded. Fingerstick blood glucose (FSBG) data were captured using Roche ACCU-CHEK glucometers (Roche, Indianapolis, IN, USA) at screening and all subsequent clinic visits, while HbA1c was measured at screening and wk 12 and 24 by central laboratories blinded to treatment. Adverse events were monitored from baseline to 7 days after the last treatment visit.

Ethical approval according to local regulations was obtained from independent ethics committees and/or institutional review boards for all study sites. Conduct of the study was compliant with standards of data collection for clinical trials (Clinicaltrials.gov: NCT00993473), according to the Declaration of Helsinki. Written informed consent was obtained from the parent/legal guardian of each participant.

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Objectives

The primary efficacy endpoint was to compare the effect of once-daily insulin glargine dosed in the morning vs. once- or twice-daily NPH insulin on the composite hypoglycemia rate consisting of (i) symptomatic hypoglycemia episodes, which were recorded in patient diaries, then validated by study investigators; (ii) low CGM glucose excursions (<3.9 mmol/L), which were confirmed by FSBG <3.9 mmol/L 10 min before to 10 min after the low CGM excursion (i.e., confirmed low CGM); and (iii) FSBG <3.9 mmol/L, which was recorded ≥1 h from the end of a confirmed low CGM excursion. Double-counting of hypoglycemic events was avoided by not counting any event that occurred in the hour following an earlier, counted event.

Secondary endpoints included rates of severe symptomatic hypoglycemia, nocturnal hypoglycemia, nocturnal symptomatic hypoglycemia, and severe nocturnal symptomatic hypoglycemia; HbA1c values at study end; change in HbA1c values from baseline; and HbA1c <7.5% rates at study end. Severe hypoglycemia was defined as an event requiring assistance from another person, as a result of altered consciousness, to administer carbohydrate, glucagon, or to take other actions. Nocturnal events were those beginning between 23:00 hours and 7:00 hours.

Main secondary endpoints based on CGM values were (i) average daily blood glucose at study end and change from baseline; (ii) average daily blood glucose over the entire study; and (iii) blood glucose variability (including nocturnal).

Statistical analyses

Analysis was performed on the modified intent-to-treat population, defined as all randomized patients who received at least one dose of study medication. No per-protocol population was defined.

Sample size calculation was based on an expected composite hypoglycemia rate of 0.8 events/100 patient-yr of exposure to insulin glargine or to NPH insulin. The sample size and novel composite outcome was planned to ensure sufficient power so that the upper bound of the two-sided 95% confidence interval (CI) for the insulin glargine:NPH ratio of the mean composite hypoglycemia rates for the comparison of treatment groups would not exceed 1.15. A sample size of 35 completed patients per treatment group was to provide 96% power to demonstrate noninferiority of insulin glargine vs. NPH. A sequential, stepwise, closed-testing approach was used to assess noninferiority and superiority [if the upper bound of the 95% CI for the ratio of rates of the primary composite endpoint for insulin glargine to NPH insulin was <1.15 (noninferior) or <1.0 (superior)]. One-sided tests were performed at the 0.025 level of significance.

Details regarding calculation of the primary composite endpoint, and statistical models used for comparisons of the two treatment arms and endpoint analyses are described in the Appendix S1, Supporting Information.

Results

A total of 165 patients were screened and 125 patients were randomized to treatment; 61 to insulin glargine and 64 to NPH insulin (Fig. 1). One patient randomized to NPH insulin was actually treated with insulin glargine, thus the safety population comprised 62 patients for insulin glargine and 63 for NPH insulin. More patients in the NPH insulin group (10/64, 15.6%) than in the insulin glargine group (4/61, 6.6%) prematurely discontinued the study. The CGM device
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Table 1. Baseline characteristics

|                      | Insulin glargine (n = 61) | NPH insulin (n = 64) | Total (N = 125) |
|----------------------|---------------------------|----------------------|-----------------|
| **Age, yr**<br>Mean (SD) | 4.3 (0.9)                 | 4.1 (1.0)            | 4.2 (1.0)       |
| Median (range)       | 5.0 (2–5)                 | 4.0 (1–6)            | 4.0 (1–6)       |
| **Age group, n (%)**<br>≤3 yr | 10 (16.4)                 | 17 (26.6)            | 27 (21.6)       |
| >3 yr                | 51 (83.6)                 | 47 (73.4)            | 98 (78.4)       |
| **Gender, n (%)**<br>Male   | 32 (52.5)                 | 30 (46.9)            | 62 (49.6)       |
| Female               | 29 (47.5)                 | 34 (53.1)            | 63 (50.4)       |
| **Race, n (%)**<br>White   | 53 (86.9)                 | 48 (75.0)            | 101 (80.8)      |
| Black                | 2 (3.3)                   | 2 (3.1)              | 4 (3.2)         |
| Asian                | 4 (6.6)                   | 11 (17.2)            | 15 (12.0)       |
| Other                | 2 (3.3)                   | 3 (4.7)              | 5 (4.0)         |
| **Diabetes duration, yr**<br>Mean (SD) | 2.1 (1.2)                 | 2.1 (1.0)            | 2.1 (1.1)       |
| Median (range)       | 1.6 (1.0–5.3)             | 2.1 (1.0–4.9)        | 1.8 (1.0–5.5)   |
| **Insulin type, n (%)**<br>Short-acting | 54 (88.5)                 | 58 (90.0)            | 112 (89.6)      |
| Basal                | 58 (95.1)                 | 57 (89.1)            | 115 (92.0)      |
| Premixed             | 5 (8.2)                   | 8 (12.5)             | 13 (10.4)       |
| **Number of daily basal insulin injections**, n (%)<br>1 | 32 (52.5)                 | 41 (64.1)            | 73 (58.4)       |
| 2                    | 21 (34.4)                 | 15 (23.4)            | 36 (28.8)       |
| ≥3                   | 5 (8.2)                   | 1 (1.6)              | 6 (4.8)         |
| **Total daily dose of basal insulin injection (U)**<br>Mean (SD) | 7.3 (4.1)                 | 7.6 (4.8)            | 7.5 (4.4)       |
| Median (range)       | 6.0 (2.0–24.0)            | 6.0 (1.5–24.0)       | 6.0 (1.5–24.0)  |
| **Total daily dose of bolus insulin injection (U)**<br>Mean (SD) | 7.1 (3.6)                 | 8.0 (7.2)            | 7.6 (5.8)       |
| Median (range)       | 7.8 (1.3–16.0)            | 7.0 (0.8–45.0)       | 7.0 (0.8–45.0)  |

*Basal/bolus insulin injection at baseline defined as the last day with basal/bolus insulin dose >0 U before first administration of study drug on or after randomization.

was worn for a mean of 82.5 days in the insulin glargine group and 76.2 days in the NPH group. Of the 111 completers (57/61, 93.4% using insulin glargine; 54/64, 84.4% using NPH insulin), 99 patients (48/61, 78.7% and 51/64, 79.7%, respectively) satisfied the protocol-required CGM performance.

Baseline characteristics were similar between groups. The mean (SD) age of participants was 4.2 (1.0) yr, and 78.4% (98/125) of patients were over 3 yr of age (Table 1). Almost all patients (115/125, 92.0%) were using basal insulin at baseline, with 33.6% (42/125) requiring ≥2 daily basal insulin injections (Table 1). A total of 56.8% (71/125) of patients were using NPH insulin, 26.4% (33/125) insulin glargine, and 14.4% (18/125) insulin detemir at baseline. By the end of the 2-wk run-in period, the majority of patients had experienced ≥1 low CGM excursion [insulin glargine, 56/61 (91.8%); NPH insulin, 59/64 (92.2%)]. Mean (SD) HbA1c was 8.0% (1.0%) in the insulin glargine group, and 8.2% (1.4%) in the NPH insulin group (Table 3).

The mean daily dose for insulin glargine was relatively stable over the 24-wk treatment period (week 1, 0.35 U/kg; week 24, 0.38 U/kg), whereas it increased for NPH insulin (week 1, 0.37 U/kg; week 24, 0.46 U/kg) (Fig. 2). All patients on insulin glargine used one basal injection in the morning, whereas over the entire treatment with NPH insulin, patients on NPH received two basal injections per day on more study days than one basal injection per day. The mean daily dose of bolus insulin in the two treatment groups was similar at week 1 (insulin glargine group, 0.41 U/kg; NPH insulin group, 0.42 U/kg) and remained practically unchanged at week 24 (insulin glargine group, 0.41 U/kg; NPH insulin group, 0.40 U/kg).

Hypoglycemia

The incidence rate of composite hypoglycemia was 1.93 mean events/100 patient-yr for insulin glargine, and 1.69 for NPH insulin. The upper bound of the 95% CIs exceeded the prespecified noninferiority margin of 1.15 [incidence ratio estimate, 1.18 (95% CI: 0.97–1.44); Table 2]; thus, the statistical criteria for noninferiority of insulin glargine to NPH insulin were not met. Of the individual components of the composite endpoint, mean events/100 patient-yr of symptomatic hypoglycemia were 0.26 with insulin glargine and 0.33 with NPH insulin (incidence ratio estimate, 0.76 [95% CI: 0.46–1.25]), and of confirmed low CGM excursions were 0.75 vs. 0.72, respectively [incidence ratio estimate, 1.06 (95% CI: 0.79–1.42)]. The rate of low FSBG values was 1.93 with insulin glargine and 1.68 with NPH insulin [incidence ratio estimate, 1.18 (95% CI: 0.96–1.45); Table 2].

Very few events of severe hypoglycemia occurred; four in the glargine group and two in the NPH group. For nocturnal hypoglycemia (‘all hypoglycemia’ that occurred between 23:00 hours and 7:00 hours), and for nocturnal symptomatic hypoglycemia, the glargine:NPH incidence ratios were 1.09 and 0.65, respectively (Table 2). There were multiple peak occurrences of composite hypoglycemia events around
Insulin glargine in young children

Table 2. Incidence and rates of hypoglycemia by type and treatment assignment

| Efficacy endpoint                        | Insulin glargine (n = 61) | NPH insulin (n = 64) | Incidence ratio estimate (SE) [95% CI] |
|-----------------------------------------|---------------------------|----------------------|---------------------------------------|
| Composite hypoglycemia*, n (%)          | 61 (100)                  | 63 (98.4)            | 1.18 (0.12) [0.97–1.44]                |
| Events/100 patient-yr, mean (SD)        | 1.93 (1.19)               | 1.69 (1.01)          |                                       |
| Symptomatic hypoglycemia, n (%)         | 40 (65.6)                 | 44 (68.8)            |                                       |
| Events/100 patient-yr, mean (SD)        | 0.26 (0.37)               | 0.33 (0.48)          | 0.76 (0.19) [0.46–1.25]                |
| Confirmed low CGM, n (%)                | 60 (98.4)                 | 61 (95.3)            |                                       |
| Events/100 patient-yr, mean (SD)        | 0.75 (0.74)               | 0.72 (0.53)          | 1.06 (0.16) [0.79–1.42]                |
| FSBG <3.9 mmol/L, n (%)                 | 61 (100)                  | 63 (98.4)            |                                       |
| Events/100 patient-yr, mean (SD)        | 1.93 (1.22)               | 1.68 (1.01)          | 1.18 (0.12) [0.96–1.45]                |
| Severe symptomatic hypoglycemia, n (%)  | 4 (6.6)                   | 2 (3.1)              |                                       |
| Events/100 patient-yr, mean (SD)        | 0.0014 (0.0055)           | 0.0007 (0.0038)      | 1.97 (1.67) [0.37–10.37]               |
| Nocturnal hypoglycemia, n (%)           | 59 (96.7)                 | 60 (93.8)            |                                       |
| Events/100 patient-yr, mean (SD)        | 0.34 (0.26)               | 0.31 (0.25)          | 1.09 (0.14) [0.84–1.40]                |
| Nocturnal symptomatic hypoglycemia, n (%)| 17 (27.9)                 | 28 (43.8)            |                                       |
| Events/100 patient-yr, mean (SD)        | 0.024 (0.054)             | 0.037 (0.068)        | 0.65 (0.25) [0.30–1.39]                |
| Severe nocturnal symptomatic hypoglycemia, n (%) | 1 (1.6)       | 0                    |                                       |
| Events/100 patient-yr, mean (SD)        | 0.0004 (0.0029)           | 0.0000 (0.0000)      | –                                     |

*Composite outcome of symptomatic hypoglycemia, confirmed low CGM excursions (<3.9 mmol/L), and low FSBG (<3.9 mmol/L).

mealtimes and before bedtime in the insulin glargine group, whereas a peak of events was seen around noontime in the NPH insulin group (Fig. 3A). Peaks of lesser magnitude than those in the insulin glargine group also occurred at mealtimes in the NPH insulin group. Low FSBG readings that were independent of confirmed low CGM or symptomatic hypoglycemia events occurred in both groups near times of the three main meals (when bolus insulin was dosed and FSBG was tested for bolus dosing) and near bedtime (Fig. 3B).

More patients in the insulin glargine group (49/61, 80.3%) than in the NPH insulin group (35/64, 54.7%) had to switch to a new basal insulin regimen from their pretrial basal insulin. In addition, more FSBG was performed overall in the insulin glargine group (mean 1056 glucose values/patient) than in the NPH insulin group (909; ratio 1.16).

Glycemic control

Patients treated with insulin glargine showed a slight decrease from baseline in HbA1c from baseline to week 24 [(LS) least squares mean, −0.048] while a slight increase from baseline in HbA1c (LS mean, 0.045) was observed in patients treated with NPH insulin. However, the LS mean difference between the two groups (−0.09) was relatively small. The proportion of patients with HbA1c values <7.5% at study end was comparable (Table 3).

Over 24 h, mean CGM glucose was lower in the insulin glargine group than in the NPH insulin group during the day, especially in the afternoon and evening, but was higher than in the NPH insulin group overnight (Fig. 3C). At study end, the average daily blood glucose was comparable between groups, albeit numerically lower in the insulin glargine group (Fig. 3D and Table 3). There was a slight difference between treatment groups in blood glucose variability or nocturnal blood glucose variability (Table 3).
Safety

The proportion of patients with treatment-emergent adverse events was similar with insulin glargine (40/62, 64.5%) and NPH insulin (43/63, 68.3%).

Discussion

PRESCHOOL is the largest prospective study to date investigating the occurrence of hypoglycemia in children with T1DM aged ≥1 to <6 yr. It compared once-daily basal insulin glargine to conventional NPH insulin therapy usually injected twice daily. The objective of the study, to compare hypoglycemia rates in this hard-to-recruit population, could only be accomplished feasibly with a composite outcome, consisting of events of symptomatic hypoglycemia, low CGM excursions, and low FSBG measurements, which was needed to provide adequate power to detect differences in hypoglycemia between regimens.

Analysis of the primary efficacy endpoint did not demonstrate noninferiority of insulin glargine to NPH insulin in the rate of composite hypoglycemia. However, in terms of the more conventional metrics included in the secondary endpoints, such as symptomatic and nocturnal symptomatic hypoglycemia, as well as severe symptomatic/nocturnal symptomatic hypoglycemia and change from baseline in HbA1c, there was a slight difference in results between treatment groups.

These results partially support those of Dixon et al. (13). In that retrospective study of 128 children aged <6 yr with T1DM, glycemic control between insulin glargine and NPH insulin was also comparable, although severe hypoglycemia episodes were decreased with glargine treatment. Earlier, in 2001, a study comparing glargine and NPH in 349 older children (5–16 yr old) with T1DM also demonstrated comparable between-treatment glycemic control, as well as comparable rates of symptomatic, severe and severe nocturnal hypoglycemia (15). Thus, the results of PRESCHOOL are generally consistent with those of earlier studies, although they are particularly valuable due to the study’s prospective design and use of CGM in a very young population. Indeed, CGM technology is relatively new in the management of T1DM and its use is not common practice (16, 17). Therefore, recent systematic reviews and meta-analyses have highlighted that evidence from randomized trials.
for the effectiveness of CGM is currently lacking, especially in children (including toddlers and preschool children) with T1DM (16, 18, 19).

Compared with NPH, which was predominantly injected twice daily, a once-daily injection of glargine was equally effective in terms of glycemic control, with a lower mean daily dose. A once-daily basal insulin could be particularly advantageous in young children such as these, who are receiving multiple daily injections as part of a basal-bolus regimen. Administering insulin injections in this population can result in problems such as lipodystrophy, injection-site pain, and bruising (14). Once-daily insulin glargine can significantly reduce the number of daily injections required compared with NPH, as previously demonstrated in a 2008 study (20), and thus the potential for injection-related side effects. In addition, once-daily injections are convenient, potentially aiding good compliance with insulin therapy.

In the insulin glargine group, there were a greater number of low FSBG values, which were not recorded at times of low CGM excursions or symptomatic hypoglycemia signals. The majority of low FSBG readings in both groups occurred near the three main mealtimes and near bedtime, and the monitoring was probably performed as part of parents’ premeal FSBG routine. It is common clinical knowledge that families introduced to a new insulin regimen test FSBG more frequently and are less likely to change the insulin dose. As more patients in the insulin glargine group had to switch to a new basal insulin regimen from their pretrial basal insulin, more FSBG was performed overall in this group (mean measurements per patient, 1056 for glargine vs. 909 for NPH).

CGM data were used to gather more information on low blood glucose. The use of CGM monitoring is a more objective means of low blood glucose detection than alternative methods, as it is independent of parental choice regarding when to check FSBG instinctively, which may be influenced by other factors such as mealtimes or recent/upcoming periods of exercise. Investigation of hypoglycemia by CGM showed a slight difference between regimens in terms of confirmed low CGM. CGM also permits an accurate assessment of daily blood glucose variability, which in this study was moderate and comparable between the treatment groups. Figure 3C clearly illustrates that the curves of mean CGM glucose over 24 h show a similar amplitude of variation for both treatment groups, with the biggest changes occurring around mealtimes. This may mean that bolus insulin, and mealtime glucose swings, played a greater role than basal insulin during the daytime in blood glucose variability, a concept supported by an earlier study in children taking bolus insulin lispro (21).

CGM curves also offer interesting insights into patterns of glycemic excursions in preschool children where parental concerns appear to be a major factor. Glucose levels appeared closest to target early in the morning but rose considerably after breakfast when many preschool children attend daycare away from direct parental supervision. Consistent with parental interventions is the rise in CGM glucose at 10 PM in the glargine group, when no meals would normally be planned. Thus, the higher overnight glucose levels with glargine may be attributed rather to parental concern about a new insulin than lacking insulin action.

Overall, CGM glucose values were lower by 0.5–2.0 mmol/L during the day with insulin glargine, at times when that group recorded more low FSBG values than the NPH group (where CGM glucose values were lower overnight). This provides an additional explanation for the excess of low FSBG values overall in the insulin glargine group. The lower glucose values in the glargine group during the day, and higher values overnight highlighted by the CGM data, provide a more detailed picture of glycemia than the HbA1c data alone.

Our results are consistent with those reported by Mauras et al. (22) where the use of CGM in young children did not provide notable improvements in glycemic control. In this study, glycemic control was suboptimal overall, with average glucose levels being above the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended age-independent postprandial target of 10 mmol/L per 180 mg/dL (23). However, both treatment groups maintained comparable control throughout the 24-wk treatment period. The between-group difference might have been greater if the mean dose of insulin glargine had risen throughout the study, as did the mean dose of NPH insulin. However, participants’ families might have been reluctant to increase insulin doses too aggressively in such young children, especially with insulin glargine, a newer, less-familiar insulin product. Another documented reason for the lack of notable improvements in glycemic control with CGM is compliance with CGM use, which is also proven to be lower in younger vs. older patients (24). In the PRESCHOOL study, CGM was in use approximately 45–50% of the time; as such, glycemic control might have been better with greater use.

The nonhypoglycemia-related adverse events were generally balanced between the two treatment groups. Those that occurred in the insulin glargine group were not generally considered related to treatment, raising no new safety concerns over use of insulin glargine in this age group. In addition, the discontinuation rate for insulin glargine-treated patients was substantially lower than for NPH-treated patients.
The PRESCHOOL study has certain limitations. Firstly, although the parallel design is more appropriate for the age group than a crossover design, multiple centers were needed, resulting in a low patient:center ratio. This adds the potential bias of center differences, which are well known in pediatric diabetes (25). In contrast, most studies in this age group have used a crossover design to leverage the low patient number. However, crossover studies in very young children can be problematic, potentially creating a period effect since preschool children (or ‘preschoolers’) grow appreciably over the course of a 6-month study. Secondly, ethical review boards made unblinded real-time CGM mandatory for this study as other measures are not wholly adequate for showing trends, predicting impending episodes of hypoglycemia, and monitoring glycemic variability (26). Parental reading of sensor glucose or CGM notification of impending low glucose may have influenced treatment during the study, as the symptomatic hypoglycemia event rate was much lower compared with other studies in this age group (7, 27). Thirdly, although the primary composite efficacy endpoint is novel and clinically relevant, it is not comparable with that of prior, similar trials. Episodes of symptomatic hypoglycemia are most reflective of true clinical hypoglycemia, and are traditionally used in clinical trials as the primary metric of hypoglycemia. Finally, it would have benefitted the study design if the bolus insulin used by the participants with either the NPH or glargine had been the same, as insulin lispro is known to have a greater and earlier insulin peak compared with regular human insulin, and a shorter duration of action (28). Despite these limitations, PRESCHOOL study data resulted in the European Medicines Agency adopting a positive opinion in 2012, recommending a change to the indication for insulin glargine to include children with diabetes mellitus aged ≥2 yr (from ≥6 yr previously).

In conclusion, in this study of young children with T1DM, statistical noninferiority of insulin glargine to NPH insulin in the rate of composite hypoglycemia – the primary efficacy endpoint – was not demonstrated. However, in this age group, where avoidance of hypoglycemia is a key consideration, the occurrence of the important metrics of symptomatic hypoglycemia, severe, nocturnal, and severe nocturnal hypoglycemia, were no worse with insulin glargine than with NPH insulin. Additional studies would be needed to rigorously demonstrate noninferiority of insulin glargine in these critical endpoints. Furthermore, glycemic control was maintained with a once-daily insulin glargine injection, compared with NPH, which was mostly injected twice daily. These results suggest that insulin glargine is a feasible basal insulin treatment alternative in this patient population, in whom administering multiple daily injections can be problematic.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Statistical analyses.

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