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A Randomized Controlled Trial Comparing Glargine U300 and Glargine U100 for the Inpatient Management of Medicine and Surgery Patients With Type 2 Diabetes: Glargine U300 Hospital Trial

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OBJECTIVE

The role of U300 glargine insulin for the inpatient management of type 2 diabetes (T2D) has not been determined. We compared the safety and efficacy of glargine U300 versus glargine U100 in noncritically ill patients with T2D.

RESEARCH DESIGN AND METHODS

This prospective, open-label, randomized clinical trial included 176 patients with poorly controlled T2D (admission blood glucose [BG] 228 ± 82 mg/dL and HbA_{1c} 9.5 ± 2.2%), treated with oral agents or insulin before admission. Patients were treated with a basal-bolus regimen with glargine U300 ($n = 92$) or glargine U100 ($n = 84$) and glulisine before meals. We adjusted insulin daily to a target BG of 70–180 mg/dL. The primary end point was noninferiority in the mean difference in daily BG between groups. The major safety outcome was the occurrence of hypoglycemia.

RESULTS

There were no differences between glargine U300 and U100 in mean daily BG (186 ± 40 vs. 184 ± 46 mg/dL, $P = 0.62$), percentage of readings within target BG of 70–180 mg/dL (50 ± 27% vs. 55 ± 29%, $P = 0.3$), length of stay (median [IQR] 6.0 [4.0, 8.0] vs. 4.0 [3.0, 7.0] days, $P = 0.06$), hospital complications (6.5% vs. 11%, $P = 0.42$), or insulin total daily dose (0.43 ± 0.21 vs. 0.42 ± 0.20 units/kg/day, $P = 0.74$). There were no differences in the proportion of patients with BG <70 mg/dL (8.7% vs. 9.5%, $P > 0.99$), but glargine U300 resulted in significantly lower rates of clinically significant hypoglycemia (<54 mg/dL) compared with glargine U100 (0% vs. 6.0%, $P = 0.023$).

CONCLUSIONS

Hospital treatment with glargine U300 resulted in similar glycemic control compared with glargine U100 and may be associated with a lower incidence of clinically significant hypoglycemia.

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Patients with uncontrolled hyperglycemia and diabetes have high risk of complications in the hospital setting (1–5). Multiple clinical trials enrolling critically ill and noncritically ill patients have shown that good glycemic control can improve clinical outcomes in the hospital (6).

Professional associations recommend insulin therapy as the preferred approach to treat patients with uncontrolled glucose levels in the inpatient setting. Randomized multicenter trials have shown that basal-bolus treatment with basal insulin (i.e., glargine U100) improves glycemic control and reduces the rate of hospital complications compared with sliding-scale regular insulin (7–9). In general surgery patients, the basal-bolus approach results in a significant reduction in a composite of hospital complications, including postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure. On the basis of these results, clinical practice guidelines have recommended the use of the basal-bolus approach as the preferred insulin regimen for the management of noncritically ill patients with diabetes (6,10,11). Despite improvement in glycemic control, up to 30% of patients in clinical trials developed hypoglycemia in the hospital, depending on their clinical characteristics (7,9,12).

Glargine U300 has been reported to have a more stable pharmacokinetic and pharmacodynamic profile and a longer duration of action than glargine U100, leading to lower within-day variability and better day-to-day reproducibility (13–15). The results of the EDITION randomized clinical trials (RCTs) with >3,500 patients demonstrated that glargine U300 resulted in similar improvement in glycemic control with a lower rate of nocturnal hypoglycemia compared with glargine U100 (16–20). The efficacy and safety of glargine U300 has been documented in ambulatory patients with type 1 and type 2 diabetes (T2D) (14,16–20); however, no previous studies have assessed the safety and efficacy of this new insulin formulation in acutely ill patients admitted to the hospital. In addition, certain features of glargine U300 need further investigation in the hospital, including *1*) prolonged duration of action, which may limit the ability to make day-to-day adjustments in insulin dosage; *2*) a steady-state insulin concentration achieved after the 2nd or 3rd day of therapy; and *3*) limited safety data in acutely ill patients with variable nutritional status. Accordingly, we designed an RCT to compare the efficacy and safety of a basal-bolus regimen with glargine U300 or glargine U100 (standard of care) in a broad population of patients with T2D admitted to the hospital.

RESEARCH DESIGN AND METHODS

Study Design and Participants

We conducted a multicenter, prospective, noninferiority randomized study at five academic hospitals in the U.S. (Grady Memorial Hospital, Emory University Hospital, and Emory University Hospital Midtown, Atlanta, GA; Cleveland Clinic Foundation, Cleveland, OH; and Hennepin County Medical Center, Minneapolis, MN). The institutional review boards at all participating institutions approved the study protocol and consent form. This trial is registered with ClinicalTrials.gov, number NCT03013985.

Owing to the inpatient design of this study, there was no run-in period. Subjects were screened upon arrival to the emergency department or medical or general surgical wards. We enrolled adult patients (>18 years of age) with a known history of T2D treated with diet alone, any combination of oral antidiabetes agents, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) (except long-acting GLP-1 RAs), or insulin therapy (except degludec or glargine U300) admitted to a general medicine or surgical service at the participating hospitals. There was no upper limit on home insulin dose. At randomization, subjects had a blood glucose (BG) of >140 mg/dL and <400 mg/dL, without laboratory evidence of diabetic ketoacidosis (bicarbonate <18 mEq/L, pH < 7.30, or positive serum or urinary ketones). We excluded patients with history of diabetic ketoacidosis, type 1 diabetes, or hyperglycemia without a known history of diabetes as well as patients admitted to or expected to require admission to an intensive care unit, on corticosteroid therapy with >5 mg/day of prednisone equivalent, with clinically relevant hepatic disease or impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m^2), with pregnancy/breastfeeding, on parenteral nutrition or immunosuppressive treatment, or with a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study. After approval by the primary care team, patients meeting criteria were approached for enrollment. All participants provided written informed consent before the start of any trial-related procedures.

Randomization and Masking

Participants and investigators were not masked to treatment allocation. A statistician provided a computer-generated block randomization table to research pharmacists at each institution, to assign patients (1:1) with block stratification according to prior insulin use at home. Patients were randomly assigned to one of two treatment regimens: either glargine U300 or glargine U100 once daily. All patients were managed for medical and surgical conditions by the primary hospital team.

Procedures

Patients were treated with a basal-bolus insulin regimen approach as previously reported (see Supplementary Data) (9,12,21). In brief, subjects treated with insulin before admission received 80% of the total daily outpatient insulin dose. Insulin-naive patients discontinued oral agents and received a starting total daily dose (TDD) of 0.4 units/kg/day for BG between 140 and 200 mg/dL and 0.5 units/kg/day for BG between 201 and 400 mg/dL. The starting TDD was reduced to 0.3 units/kg/day for patients older than 70 years or for those with impaired renal function (eGFR 30–60 mL/min per 1.73 m^2). Half of the TDD was administered as once-daily basal insulin (glargine U300 or U100) and half as prandial insulin (glulisine) divided in three equal doses before meals.

Owing to the lack of efficacy and safety data with the use of glargine U300 in the inpatient setting, periodic interim analyses were conducted every 6 months to monitor the primary outcome and rate of hypoglycemia and to modify the study design regarding interval of administration and dosage adjustment for basal insulin. On the original protocol design, glargine U300 and U100 were given once daily, at the same time of the day. Insulin doses were adjusted daily to maintain a fasting and predinner BG between 100 mg/dL and 180 mg/dL. If the fasting and predinner BG was between 100 and 180 mg/dL in the absence of hypoglycemia, no change was made. Basal insulin was increased by 10% if the premeal BG was between 180 and 240 mg/dL and by

20% if the BG was >240 mg/dL. After a prespecified interim analysis conducted at 6 months, the protocol was modified on 12 October 2017 (14 participants randomized to U100 and 18 randomized to U300) to adjust basal and supplemental rapid-acting insulin doses on a daily basis for BG values >140 mg/dL as opposed to 180 mg/dL (9,12,21). The TDD was increased by 10% if BG was between 140 and 180 mg/dL, by 20% if BG was between 180 and 240 mg/dL, and by 30% if BG was >240 mg/dL (9,12,21).

Glucose Monitoring

Glucose levels were assessed by capillary point-of-care (POC) testing before meals and bedtime. A subgroup of participants ($n = 82$) wore a professional (blinded) Abbott FreeStyle Libre continuous glucose monitor (CGM).

Efficacy Outcomes

The primary end point of the study was to determine whether the use of glargine U300 was noninferior to the use of glargine U100 (standard of care) for glycemic control in the hospital, as measured by mean daily BG levels. Primary and secondary end points relating to glycemic control were assessed during the first 10 days after randomization. We determined differences in mean daily glucose in patients admitted to medicine and surgery services, mean BG in patients with variable length of stay (shorter and longer than 3 and 5 days), mean BG according to HbA_{1c} (higher or lower than 8%), and the proportion of BG readings within target (70–180 mg/dL) before meals. Participants with persistent hyperglycemia (two or more glucose readings ≥400 mg/dL, three or more consecutive glucose readings >280 mg/dL, or a mean daily BG concentration ≥280 mg/dL) were considered treatment failure. Glucose values obtained with CGM were analyzed to compare the percentage of time that the sensor glucose measurement was within the target range (70–180 mg/dL) or above the target range (181–250 mg/dL and >250 mg/dL). Glycemic variability was determined by the coefficient of variation of glucose values.

Adverse Events and Safety

We determined the number of patients with hypoglycemia as defined by the Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, defined as glucose <70 mg/dL, clinically significant hypoglycemia (<54 mg/dL), or severe hypoglycemia (<40 mg/dL) (6,22). In addition, glucose values obtained with CGM were analyzed to compare the percentage of time that the sensor glucose measurement was below the target range (54–69 mg/dL and <54 mg/dL) (23). A set of hospital complications was investigated, including cardiovascular complications (myocardial infarction, cardiac arrhythmia requiring medical treatment, or cardiac arrest), renal failure (defined as an increment in serum creatinine >0.5 mg/dL from baseline), respiratory failure, infections, and mortality.

Statistical Analysis

Noninferiority for the primary end point of glycemic control was defined as a mean BG difference of <18 mg/dL between glargine U300 and glargine U100 (7,9,12,24). A BG difference of such a magnitude has been reported in other superiority trials as nonclinically significant and is smaller than significant treatment effects (12,25). Assuming the true BG difference between the treatment groups is zero, and using one-sided, two-sample *t* tests, we required 78 subjects for each treatment group to achieve 80% power. Accounting for a 10% attrition rate, we aimed to enroll 180 subjects in total to achieve >80% power. To compare baseline and clinical characteristics and outcomes, such as mean daily BG, occurrence of hypoglycemia, and occurrence of complications between treatment groups, we used nonparametric Wilcoxon tests for continuous variables and χ^2 tests (or the Fisher exact test) for discrete variables. To determine differences in the primary end point, we performed a cross-sectional analysis using nonparametric Kruskal-Wallis tests (or Wilcoxon tests) or one-way ANOVA, followed by repeated-measures ANOVA to estimate and test the difference between the two treatment groups while simultaneously examining mean daily BG across multiple days during treatment. Secondary end point analysis was not adjusted for multiple comparisons. A *P* value of <0.05 was considered significant. The data are presented as mean ± SD for continuous variables and count (percentage) for discrete variables. We performed the statistical analyses with SAS 9.4 software.

RESULTS

Between 17 May 2017 and 22 March 2019, we approached 247 eligible patients admitted to general medicine and surgery services. Of these, 238 patients agreed to participate and were randomized to receive glargine U300 or glargine U100. In the glargine U300 group, 16 patients were excluded from the analysis because they stayed in the hospital <24 h after study enrollment ($n = 14$)

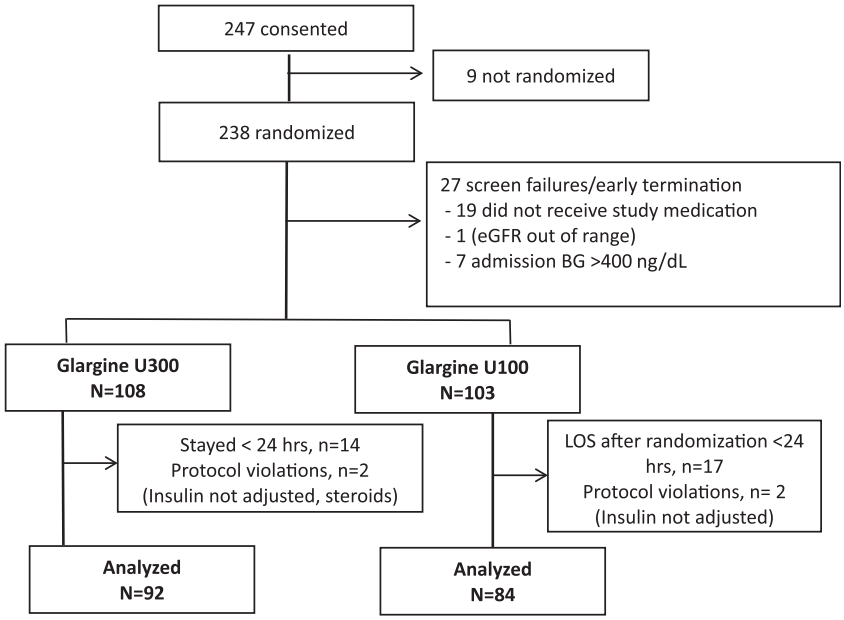

Figure 1—Study flow. LOS, length of stay.

and 2 due to protocol violations (insulin not adjusted [$n = 1$] and exposure to high-dose glucocorticosteroids [$n = 1$]). In the glargine U100 group, 19 patients were excluded from the analysis because they stayed in the hospital <24 h after study enrollment ($n = 17$) or due to protocol violations ($n = 2$); therefore, 92 patients in the glargine U300 group and 84 in the glargine U100 group were included in the analysis (Fig. 1). Baseline characteristics were similar, without significant differences in age, race/ethnicity, BMI, duration of diabetes, admission service, mean admission glucose concentration, baseline HbA_{1c}, or outpatient antidiabetes treatment (Table 1). The median inpatient stay was 6 days (interquartile range [IQR] 4.0, 8.0) in glargine U300 patients versus 4.0 days (IQR 3.0, 7.0) in glargine U100 patients ($P = 0.06$). No significant difference in glycemic control was observed in patients with variable length of stay. The proportion of patients with eGFR <60 mL/min per 1.73 m^2 was similar in both groups (30% in glargine U300 and 28% in glargine U100). Mean BG for the study participants ($n = 32$) before the amendment was 193 ± 41 compared with 188 ± 39 after the amendment ($P = 0.46$).

Both treatment regimens resulted in similar improvement in mean daily BG concentrations during the hospital stay (a maximum duration of treatment of 10 days) (Fig. 2). The mean daily BG concentration in the glargine U300 group was not inferior to that in the glargine U100 group (186 ± 40 mg/dL vs. 184 ± 46 mg mg/dL), with a mean BG difference of 2.49 mg/dL (95% CI −10.27 to 15.25) (Table 2).

No differential effect on efficacy (achieving a BG concentration between 70 and 180 mg/dL) was observed for patients with either HbA_{1c} <9% (odds ratio [OR] 1.49, 95% CI 0.65–3.44) or ≥9% (OR 1.32, 95% CI 0.55–3.20; reference group: glargine U300; P for interaction = 0.84). No center effect was observed on mean BG ($P = 0.2$) or hypoglycemia ($P = 0.06$).

There were no differences in the number of patients with BG <70 mg/dL between groups by capillary POC testing. Clinically significant hypoglycemia (<54 mg/dL) was infrequent but occurred more commonly among patients treated with glargine U100 (6.0%) compared with participants receiving glargine U300 (0%) (Fig. 3). One episode of severe hypoglycemia (<40 mg/dL) occurred in the glargine U100 group.

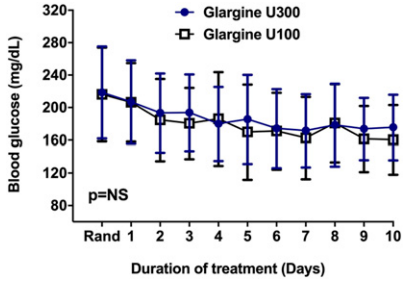

Figure 2—Mean daily BG concentrations measured in patients treated with glargine U300 or glargine U100. Data are mean ± SD.

In the subset of patients using the professional CGM, no significant differences in glycemic control between groups were observed by CGM metrics (Supplementary Table). The U300 and U100 glargine groups both spent a similar percentage of time in target glucose range and had comparable glycemic variability, time above target range (181–250 mg/dL), and rates of severe hyperglycemia (>250 mg/dL). Additionally, similar percentages of time below target glucose range (54–69 mg/dL) were observed in the U300 glargine group compared with the U100 glargine group, without a significant difference in the percentage of time with clinically important hypoglycemia (<54 mg/dL). Overnight (2200–0600 h) time below range was lower but nonsignificant with U300 compared with U100 (Supplementary Table).

Table 1—Baseline characteristics

	Glargine U300 ($n = 92$)	Glargine U100 ($n = 84$)	P value
Age, years	57.6 ± 11.4	55.60 ± 12.61	0.26
Sex female	39 (42)	26 (31)	0.16
BMI, kg/m^2	34.1 ± 9.5	33.8 ± 8.7	0.80
Race African American	60 (65)	52 (62)	0.62
Duration of diabetes, years	10.5 ± 9.7	9.9 ± 8.1	0.92
Admission BG, mg/dL	236.8 ± 85.2	219.4 ± 77.8	0.21
Randomization BG, mg/dL	218.7 ± 56.8	216.4 ± 57.7	0.73
A1C, %	9.4 ± 2.2	9.5 ± 2.2	0.9
Admission service			0.35
Medicine	62 (67)	62 (74)	
Surgery	30 (33)	22 (26)	
Home regimen			
Metformin	46 (50)	39 (46)	0.64
Sulfonylureas	8 (8.7)	11 (13)	0.47
Secretagogues	0 (0)	1 (1.2)	0.47
DPP-4 inhibitors	6 (6.5)	8 (9.5)	0.58
GLP-1 RAs	2 (2.2)	4 (4.8)	0.43
SGLT-2 inhibitors	1 (1.1)	2 (2.4)	0.61
Glargine U100	30 (33)	37 (44)	0.12
Levemir	16 (17)	13 (15)	0.73
Insulin NPH	2 (2.2)	2 (2.4)	0.99
Insulin regular	4 (4.3)	1 (1.2)	0.37
Insulin aspart/lispro/glulisine	33 (36)	30 (36)	0.98
Premixed insulin 70/30	6 (6.5)	6 (7.1)	0.99

Continuous data are presented as the mean ± SD and discrete data as n (%). DPP-4, dipeptidyl peptidase 4; SGLT-2, sodium–glucose cotransporter 2.

CONCLUSIONS

The results of our study support the hypothesis that the use of glargine U300 is as effective as glargine U100 for the management of hyperglycemia in noncritically ill patients with T2D admitted to medical or surgical services. Our findings also expand upon previous data showing that glargine U300 may decrease the risk of hypoglycemia compared with glargine U100 (16–20).

Basal insulin use represents the mainstay of therapy in the hospital setting (6). Previous studies with different basal insulins have shown the efficacy of scheduled basal-bolus regimens for the management of hyperglycemia (9,12,25). Glargine U300 is a recently approved ultralong basal insulin with different pharmacokinetics compared with glargine U100. Given its longer half-life, uncertainty about

Table 2—Glycemic data, length of stay, and hospital complications

	Glargine U300 (n = 92)	Glargine U100 (n = 84)	P value
Daily BG by POC, mg/dL	186 ± 40	184 ± 46	0.62
BG 70–180 mg/dL by POC, %	50.3 ± 27.5	54.9 ± 29.3	0.30
Insulin TDD, units/kg/day	0.43 ± 0.2	0.42 ± 0.2	0.70
Insulin TDD, units/day	43.9 ± 25.4	42.8 ± 22.4	0.99
Basal insulin, units/day	29.0 ± 17.1	28.3 ± 14.4	0.87
Prandial insulin, units/day	14.4 ± 9.3	13.3 ± 8.7	0.57
Supplemental insulin, units/day	7.6 ± 3.6	7.5 ± 4.1	0.43
Any BG <70 mg/dL by POC	8 (8.7)	8 (9.5)	0.99
Any BG <54 mg/dL by POC	0 (0)	5 (6.0)	0.02
Treatment failure	18 (19.6)	9 (10.7)	0.14
Length of stay, days	6.0 (4.0, 8.0)	4.0 (3.0, 7.0)	0.07
Composite of complications	6 (6.5)	9 (11)	0.42

Continuous data are presented as the mean ± SD or median (IQR) and discrete data as n (%). Treatment failures were considered if there was persistent hyperglycemia (two or more glucose readings ≥400 mg/dL, three or more consecutive glucose readings >280 mg/dL, or mean daily BG concentration ≥280 mg/dL).

the adjustment of glargine U300 doses in the hospital remains. Our study shows that dose adjustments following the same protocol of insulin adjustment with glargine U100 result in similar glycemic control without an increase in hypoglycemia risk. This has relevant implications, particularly because many patients using glargine U300 in the ambulatory setting will likely require basal insulin coverage if admitted to the hospital and may continue the same therapy if available. In addition, glargine U300 may decrease the risk of clinically important hypoglycemia in the hospital.

In the ambulatory setting with observations over several weeks, patients receiving glargine U300 may require higher doses (~10%) than patients receiving U100 to achieve similar efficacy. We did not observe such difference between treatment groups in this study, which may be related to the short period of observation.

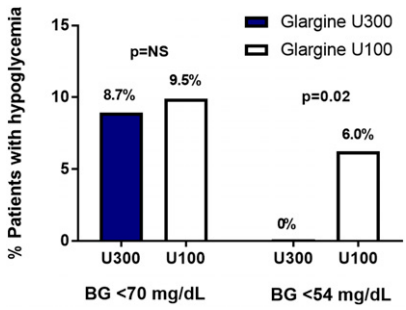

Figure 3—Proportion of patients with hypoglycemic episodes by POC testing.

The fact that glargine U300 has consistently shown a reduction in the risk of hypoglycemia provides a potential advantage, particularly for patients at higher risk for hypoglycemia (i.e., elderly patients, chronic kidney disease) (26). In agreement with these studies, we observed a significantly lower incidence of clinically important hypoglycemia (<54 mg/dL) among those treated with glargine U300 (0 vs. 6%) compared with patients treated with the glargine U100 formulation. However, in a subgroup of patients wearing CGMs, we did not observe the difference of clinically significant hypoglycemia (<54 mg/dL) with CGMs. The overall time below range represented by the proportion of glucose values <54 mg/dL and overnight (2200–0600 h) time below range were lower but not statistically significant for patients randomized to glargine U300. Of interest, a recent smaller RCT (n = 74) examined the efficacy of the other available long-acting insulin degludec compared with glargine U100 in patients with T2D admitted for glycemic control optimization (27). The authors reported similar improvement in glycemic control and similar risk of hypoglycemia with both insulin formulations; however, the number of hypoglycemic events was very small. No head-to-head comparisons of these two longer-acting insulins (degludec vs. glargine U300) have been reported in the inpatient setting (28).

The results of multiple clinical trials in the hospital setting suggest that patients with diabetes may respond differently to a commonly used basal-bolus approach (7,9,12,24,25,29). Patients with higher HbA_{1c} levels on admission, for example, may have a lower risk of hypoglycemia as well as a lower probability of achieving glycemic goals with a standard basal-bolus strategy in the hospital (29). In the present clinical trial, ~50% of participants achieved glycemic targets in both treatment groups. These values are lower than in previous RCTs (9,12,24,25). The higher daily BG could be explained by enrolling patients with poor glycemic control with an average admission BG of 229 ± 82 mg/dL and HbA_{1c} of 9.5 ± 2.2%, most of them receiving insulin before admission. In addition, during the first 6 months of the study, because of concerns of hypoglycemia using the concentrated and longer-acting glargine U300, we did not adjust basal insulin unless BG was >180 mg/dL compared with previous studies where the TDD was adjusted when BG was >140 mg/dL before meals (6,9,12,24,25,30). These modifications to the protocol may explain the higher mean daily BG concentration in this study compared with previous RCTs. A more aggressive approach, however, may increase significantly the risk of hypoglycemia. In a study that included a wide variety of patients, we observed a high incidence of hypoglycemia (~37.3%) with both insulin analogs and human insulins despite a reduction of 20% of the TDD for participants treated with insulin at home (including patients receiving >0.5 units/kg/day) (7).

There are limited prospective efficacy and safety data for most noninsulin agents in the hospital, including GLP-1 RAs (31). We excluded patients treated with long-acting GLP-1 RAs in this study because all noninsulin agents were discontinued on admission. We also wanted to minimize the potential bias of changes in GLP-1 RA concentrations after discontinuation of long-acting agents. Recent pilot data suggest that the combination of a GLP-1 RA with basal insulin may be effective in the hospital but associated with an expected increase in gastrointestinal adverse effects (32).

We acknowledge additional limitations to our study. The study was not powered to examine differences in complications between groups. Nevertheless, there was no signal of increased risk of complications with the use glargine U300 (7%) compared with glargine U100 (11%). The

characteristics of patients enrolled in this trial are different from previous inpatient trials from our group in that we enrolled a very broad group of patients with uncontrolled diabetes, many of them with very high HbA_{1c}; thus, these findings may not be applicable to patients with mild hyperglycemia. Furthermore, our strategy of daily insulin titration with close monitoring of glucose levels and kidney function may not apply to ambulatory patients. A much more conservative patient-driven titration algorithm of 1 unit/day of glargine U300 may be safer and effective in a primary care setting (33). Our findings are not applicable to patients taking high doses of steroids and immunosuppressants in the hospital. There was a nonsignificant imbalance on length of stay between groups. A larger sample size may be warranted to provide a more confirmative conclusion. In addition, the use of the FreeStyle Libre CGM was exploratory. It is also not clear whether the calculated average (lower estimated mean BG with CGM compared with POC in this study) is an accurate reflection of glucose levels in the hospital. A preliminary analysis comparing POC with CGM in the hospital suggested lower accuracy with FreeStyle Libre CGM for glucose readings of $<$70 mg/dL (34). Ongoing studies are further evaluating other CGM devices in the hospital setting (reg. nos. NCT03877068, NCT03832907, NCT03508934, ClinicalTrials.gov).

Conclusion

In conclusion, the use of glargine U300 in the hospital setting is as effective as glargine U100 for the management of medical and surgical patients with T2D. In addition, the use of glargine U300 may decrease the incidence of hypoglycemia in this population.

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