Efficacy and Safety of Intensive Versus Nonintensive Supplemental Insulin With a Basal-Bolus Insulin Regimen in Hospitalized Patients With Type 2 Diabetes: A Randomized Clinical Study

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OBJECTIVE

Administration of supplemental sliding scale insulin for correction of hyperglycemia in non–intensive care unit (ICU) patients with type 2 diabetes is frequently used with basal-bolus insulin regimens. In this noninferiority randomized controlled trial we tested whether glycemic control is similar with and without aggressive sliding scale insulin treatment before meals and bedtime in patients treated with basal-bolus insulin regimens.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes with admission blood glucose (BG) 140–400 mg/dL treated with basal-bolus insulin were randomized to intensive (correction for BG >140 mg/dL, *n* = 108) or to nonintensive (correction for BG >260 mg/dL, *n* = 107) administration of rapid-acting sliding scale insulin before meals and bedtime. The groups received the same amount of sliding scale insulin for BG >260 mg/dL. Primary outcome was difference in mean daily BG levels between the groups during hospitalization.

RESULTS

Mean daily BG in the nonintensive group was noninferior to BG in the intensive group with equivalence margin of 18 mg/dL (intensive 172 ± 38 mg/dL vs. nonintensive 173 ± 43 mg/dL, *P* = 0.001 for noninferiority). There were no differences in the proportion of target BG readings of 70–180 mg/dL, <70 or <54 mg/dL (hypoglycemia), or >350 mg/dL (severe hyperglycemia) or total, basal, or prandial insulin doses. Significantly fewer subjects received sliding scale insulin in the nonintensive (*n* = 36 [34%]) compared with the intensive (*n* = 98 [91%] [*P* < 0.0001]) group with no differences in sliding scale insulin doses between the groups among those who received sliding scale insulin (intensive 7 ± 4 units/day vs. nonintensive 8 ± 4 units/day, *P* = 0.34).

CONCLUSIONS

Among non-ICU patients with type 2 diabetes on optimal basal-bolus insulin regimen with moderate hyperglycemia (BG <260 mg/dL), a less intensive sliding scale insulin treatment did not significantly affect glycemic control.

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Hyperglycemia in the inpatient setting is an independent predictor of mortality and increases length of stay and complications such as surgical site infections (1–7). The basal-bolus plus supplemental insulin regimen, consisting of once daily long-acting insulin with rapid-acting insulin for meals with supplemental rapid acting insulin for hyperglycemia correction, is recommended as the treatment for hyperglycemia in patients with type 2 diabetes admitted to the general medical and surgical floors (8,9). Basal-bolus plus supplemental insulin regimens have been shown to reduce the rate of hospital complications in patients with type 2 diabetes (3,10,11). The basal-bolus insulin regimen with supplemental sliding scale has been adapted from principles of outpatient treatment for type 1 diabetes to replicate physiologic insulin responses. However, hospitalized patients with type 2 diabetes may have variable insulin secretion and likely do not need regimens that are similar to those needed for type 1 diabetes. Despite basal-bolus with supplemental sliding scale insulin being recommended in guidelines, the basal-bolus regimen is underutilized (12–15). Addition of supplemental insulin to a basal-bolus insulin regimen in type 2 diabetes could improve glycemic control but may increase treatment burden with additional insulin dose calculations/injections and is associated with the 16–40% of iatrogenic hypoglycemia seen in studies with use of basal-bolus insulin regimens (3,10,11).

The threshold glucose level at which supplemental insulin needs to be added onto bolus insulin doses is not known. Previous studies have used a threshold blood glucose (BG) level $>$ 140 mg/dL for addition of supplemental insulin (3,8,11), potentially explaining the iatrogenic hypoglycemia. We showed that a less aggressive supplemental insulin at bedtime did not change fasting glucose or mean daily glucose levels in hospitalized non–intensive care unit (ICU) patients with type 2 diabetes treated on a basal-bolus insulin regimen (16). The benefits and risks of a less aggressive supplemental insulin before meals and bedtime in hospitalized patients with type 2 diabetes treated with a basal-bolus insulin regimen have not been tested in a randomized clinical trial (RCT). Accordingly, in this RCT we aimed to determine whether intensive supplemental sliding scale insulin treatment before meals and bedtime results in glycemic control similar to that with less aggressive or nonintensive sliding scale insulin treatment in non-ICU patients with type 2 diabetes. We hypothesized that in hospitalized patients with type 2 diabetes treated with optimal basal-bolus therapy, there will be no difference in mean glucose levels between intensive or nonintensive supplemental sliding scale insulin for mild-to-moderate hyperglycemia.

RESEARCH DESIGN AND METHODS

This randomized open-label study (clinical trial reg. no. NCT02408120, ClinicalTrials.gov) was conducted at Emory University at Emory University Midtown Hospital and Grady Memorial Hospital, Atlanta, GA. The study was approved by Emory University Institutional Review Board.

Inclusion and Exclusion Criteria

Patients hospitalized with a diagnosis of type 2 diabetes for $>$3 months, aged 18–80 years, presenting with BG 140–400 mg/dL (7.8–22.2 mmol/L), and treated at home with diet, oral antidiabetes agents, noninsulin injectable therapy, or insulin therapy were included in the study. Patients were excluded if they had a diagnosis of type 1 diabetes, diabetic ketoacidosis, or BG $>$400 mg/dL (22.2 mmol/L) on admission; were on glucocorticoid therapy when admitted to the ICU or on continuous insulin infusion; had clinically relevant hepatic or renal disease; or were pregnant or unable to give consent.

Randomization and Masking

Randomization tables were stratified by BG above or below 200 mg/dL. The data were, was computer generated and provided by Rollins School of Public Health. Randomization was performed by a research coordinator who was not involved in the study. All subjects consented and were randomized to either intensive supplement or nonintensive supplement groups.

Study Protocol

All randomized subjects had home antidiabetes medications discontinued on randomization. Basal-bolus insulin therapy was initiated as per previous studies (3,10,11,16). For insulin-naïve subjects, total daily insulin dose was calculated as follows: randomization BG 140–200 mg/dL (7.8–11.1 mmol/L), total daily insulin dose started at 0.4 units/kg/day, and randomization BG 201–400 mg/dL (11.2–22.2 mmol/L), total daily insulin doses started at 0.5 units/kg/day. One-half of the total daily dose was given as basal insulin with glargine or detemir once daily and the other half given as rapid-acting insulin (lispro or aspart) equally divided before three meals. For subjects on insulin therapy at home, insulin dose was decreased to 80% of home dose. Basal and bolus doses were actively titrated daily as outlined in Supplementary Material.

Supplemental insulin doses are listed in Supplementary Table 1. Subjects in the nonintensive supplement group did not receive any supplemental sliding scale insulin for BG $<$260 mg/dL (14.4 mmol/L), while subjects in the intensive supplement group received sliding scale insulin for BG $>$ 140 mg/dL (7.8 mmol/L) as per previous protocol (11). Both groups received supplemental insulin for BG $>$260 mg/dL. Supplemental sliding scale insulin was administered based on sensitive/usual/resistant scale as outlined in Supplementary Material. All subjects were started on the usual supplemental sliding scale unless they had a randomization BG $>$260 mg/dL. If randomization BG was $>$260 mg/dL, a resistant sliding scale was initiated. If any subjects were anticipated to be fasting or had hypoglycemia, a sensitive sliding scale was initiated. The usual supplemental sliding scale was as follows for the intensive group: BG 141–180 mg/dL (7.8–10 mmol/L), 3 units; 181–220 mg/dL (10.1–12.2 mmol/L), 4 units; 221–260 mg/dL (12.3–14.4 mmol/L), 5 units; 261–300 mg/dL (14.5–16.7 mmol/L), 6 units; 301–350 mg/dL (16.7–19.4 mmol), 8 units; 351–400 mg/dL (19.5–22.2 mmol/L), 10 units; and $>$400 mg/dL (22.2 mmol/L), 12 units. The cutoff for receiving supplemental insulin of BG $>$260 mg/dL (14.4 mmol/L) in both was based on studies with findings that threshold glucose $>$250 mg/dL (13.9 mmol/L) was associated with increased rate of hospital complications (17). Due to safety concerns and for consistency with the cutoff for use of supplemental sliding scale insulin in our previous studies (10,11,16), we used 260 mg/dL (14.4 mmol/L).

Once randomized, order sets in the electronic medical record were placed by a study investigator with appropriate initial insulin doses and supplemental sliding scale for each treatment group.

Both groups had point of care testing performed prior to each meal and bedtime. Both groups had basal and prandial insulin doses titrated daily by study physicians to a target BG between 70 and 140 mg/dL (3.9 and 7.8 mmol/L) as outlined in a previous study (16) and referenced in Supplementary Material. Since the primary responsibility for the patient is with the general medicine or surgical team, the primary teams were allowed to change insulin doses if meal frequency and quantity were expected to change.

Statistical Analysis

The primary outcome was the difference in mean daily BG levels during the hospital stay. Secondary outcomes were percentage of time spent in a state of hypoglycemia, defined as BG <70 mg/dL (3.9 mmol/L) and BG <54 mg/dL (3.0 mmol/L); percentage of time in a state of hyperglycemia, defined as BG > 260 mg/dL (14.4 mmol/L) and BG > 350 mg/dL (19.4 mmol/L); percentage of time with BG 140–260 mg/dL (7.8–14.4 mmol/L); daily total, basal, prandial, and supplemental sliding scale insulin doses; and a composite of hospital complications, defined as acute kidney injury, infection, pneumonia, and death. Mean BG levels were calculated as the average daily glucose levels divided by the number of days. Since subjects would not have received study intervention on the day of randomization, calculations were performed starting on day 2. Acute kidney injury was defined as serum creatinine increase >0.5 mg/dL over admission creatinine. Otherwise, subjects in the nonintensive supplement group did not receive any supplemental insulin when not indicated according to protocol.

We performed post hoc analyses where we stratified subjects by BG levels between 140 and 260 mg/dL (7.8 and 14.4 mmol/L) and without any BG >260 mg/dL (14.4 mmol/L) and those with at least one BG >260 mg/dL (14.4 mmol/L) after randomization. Differences in mean BG, total daily insulin dose, and supplemental sliding scale insulin were calculated between the intensive and the nonintensive supplement groups.

For continuous variables data are expressed as mean and SD unless otherwise noted. Discrete variables data are expressed as a number with percentage. Kruskal-Wallis tests were used for comparisons of continuous variables, and χ^2 tests were used for comparisons of discrete variables. Noninferiority testing was conducted based on the one-sided *t* test with the equivalence margin set at 18 mg/dL (1 mmol/L). All analyses were performed in SAS.

Power

This was a noninferiority study design. Similar to our previous studies in inpatient diabetes, we set the equivalence margin for comparing treatment effect as 18 mg/dL (1 mmol/L). We anticipated an SD of 50 mg/dL (2.8 mmol/L). With 80% power and two-sided α of 0.05, we initially estimated that we should recruit 125 subjects in each arm. However, given that the upper bound of the observed SD of mean glucose levels during the hospital stay is bounded above by 45 mg/dL (2.5 mmol/L) in either study group, with an actual sample of at least 107 subjects in each arm, we calculated that we could achieve 83% power to detect the difference in the mean glucose levels. Therefore, the study was stopped before recruiting 125 subjects in each group.

RESULTS

The study flow is shown in Fig. 1. A total of 226 subjects consented. Two subjects withdrew or left the hospital prior to randomization. In the intensive supplement group, four subjects were excluded after randomization. In particular, one subject did not receive basal-bolus insulin due to hypoglycemia prior to initiation of protocol. In the nonintensive group, five subjects were excluded after randomization. In particular, two subjects did not receive basal-bolus insulin regimen at the discretion of the primary treating physician. A total of 108 subjects in the intensive group and 107 subjects in the nonintensive group were included in the final analysis.

Table 1 shows baseline demographics. There were no significant differences between baseline characteristics between the intensive and the nonintensive supplement groups. Both groups had mean diabetes duration of >10 years. Among patients, a majority were obese and a majority were treated with insulin at home with mean HbA_{1c} >9% (75 mmol/mol), indicating poorly controlled diabetes. Median length of stay did not differ between the groups. Home total daily insulin doses were high in both the intensive (mean ± SD 63 ± 47 units/day) and nonintensive (77 ± 53 units/day) supplement groups without a statistical difference.

Mean ± SD daily BG in the nonintensive group was noninferior to that in the intensive group with equivalence margin of 18 mg/dL (Table 2) (intensive 172 ± 38 mg/dL vs. nonintensive 173 ± 43 mg/dL, $P = 0.001$ for noninferiority). There were no differences between groups in the number of subjects with hypoglycemia with BG <70 mg/dL (3.9 mmol/L) and <54 mg/dL (3.0 mmol/L). There were no subjects with BG <40 mg/dL (2.2 mmol/L). The number of subjects with BG 140–260 mg/dL (7.8–14.4 mmol/L) and BG >260 mg/dL (14.4 mmol/L) did not differ. The percentage of subjects with BG >350 mg/dL (19.4 mmol/L) was low at 4% in the intensive and 1% in the nonintensive group without statistical difference between the groups. Forty-seven percent of the subjects in the intensive group and 39% of the subjects in the nonintensive supplement group had one or more BG >260 mg/dL (14.4 mmol/L) after randomization. Basal and prandial insulin doses did not differ between the groups. A significantly lower number and proportion of subjects received supplemental insulin in the nonintensive ($n = 36$ [34%]) compared with the intensive ($n = 98$ [91%], $P < 0.0001$) group. Among subjects who received supplemental sliding scale insulin there were no differences between groups (intensive 7 ± 4 units/day vs. nonintensive 8 ± 4 units/day, $P = 0.34$). There were no differences in complications between the groups.

Since both groups received supplemental insulin for BG >260 mg/dL, we performed a post hoc subgroup analysis (Table 3) with stratification by subjects with BG between 140 and 260 mg/dL (7.8 and 14.4 mmol/L) and those with at least one BG >260 mg/dL (14.4 mmol/L). According to the protocol, subjects in the nonintensive supplement group with BG 140–260 mg/dL did not receive any supplemental insulin. All the supplemental insulin received in the nonintensive group was accounted for by subjects who had BG >260 mg/dL. In subjects with BG 140–260 mg/dL (7.8–14.4 mmol/L), mean daily BG did not differ with the intensive supplement group receiving mean ± SD 5 ± 2 units of supplemental insulin while the nonintensive group received no supplemental insulin. There were

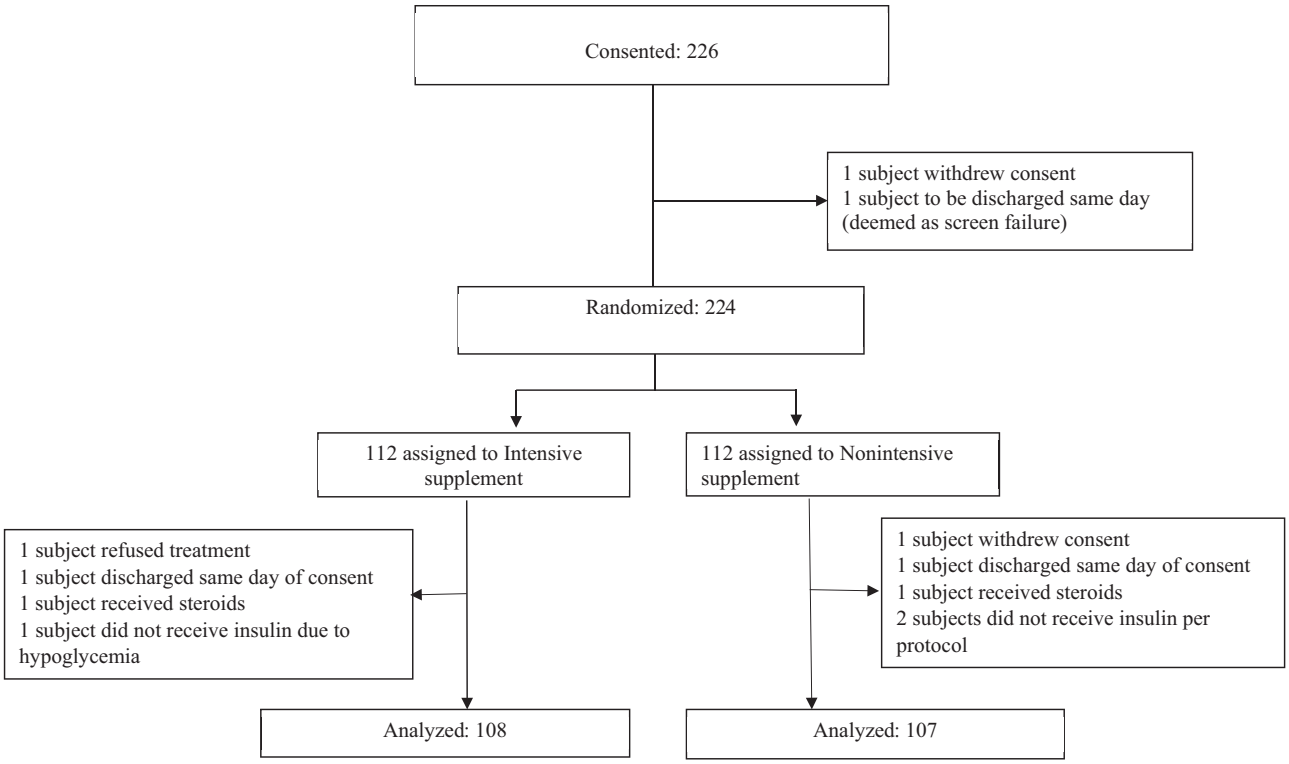

Figure 1—Study flow of subject recruitment for randomized controlled study of nonintensive vs. intensive supplemental insulin treatment.

Table 1—Demographic and baseline clinical characteristics in the intensive and nonintensive supplement treatment groups

	All (*n* = 215)	Intensive (*n* = 108)	Nonintensive (*n* = 107)	*P*
Age, years	58 ± 11	58 ± 12	59 ± 11	0.45
Sex, male/female, *n* (%)	115/100 (53/47)	57/51 (53/47)	58/49 (54/46)	0.83
Race, *n* (%)				0.25
Black	174 (81)	92 (85)	82 (77)	
White	37 (17)	15 (14)	22 (21)	
Other	4 (2)	1 (1)	3 (3)	
BMI, kg/m^2	34.4 ± 9.8	34.2 ± 8.9	34.7 ± 10.7	0.88
Weight, kg	103 ± 31	102 ± 30	103 ± 32	0.94
Diabetes duration, years	12 ± 9	12 ± 8	13 ± 9	0.32
HbA_{1c}, % (mmol/mol)	9.1 ± 2.3 (76 ± 25.1)	9.2 ± 2.3 (77 ± 25.1)	9.1 ± 2.3 (76 ± 25.1)	0.85
Admission BG, mg/dL (mmol/L)	210 ± 57 (11.7 ± 3.2)	212 ± 88 (11.8 ± 4.9)	207 ± 90 (11.5 ± 5.0)	0.68
Home diabetes treatment, *n* (%)				0.82
No treatment	53 (25)	26 (24)	27 (25)	
OAD alone	30 (14)	13 (12)	17 (16)	
OAD + insulin	17 (8)	8 (7)	9 (8)	
GLP-1RA only	1	0	1 (1)	
GLP-1RA + insulin	6 (3)	4 (4)	2 (2)	
Insulin only	108 (50)	57 (53)	51 (48)	
Home insulin dose, units/day	70 ± 50	63 ± 47	77 ± 53	0.085
Hospital service, *n* (%)				0.85
Medicine	156 (73)	79 (73)	77 (72)	
Surgical	59 (27)	29 (27)	30 (28)	
LOS, days, median (IQR)	4.0 (3.0, 8.0)	4.0 (3.0, 7.5)	4.0 (3.0, 9.0)	0.59

Data are means ± SD unless otherwise indicated. GLP-1RA, glucagon-like peptide 1 receptor agonist; IQR, Interquartile range; LOS, length of stay; OAD, oral antidiabetes agents.

Table 2—Glycemic control with intensive compared with nonintensive supplement groups

	All (*n* = 215)	Intensive (*n* = 108)	Nonintensive (*n* = 107)	*P*
Randomization BG, mg/dL (mmol/L)	222 ± 57 (12.3 ± 3.2)	226 ± 62 (12.6 ± 3.4)	218 ± 51 (12.1 ± 2.8)	0.65
Mean daily BG, mg/dL (mmol/L)	173 ± 40 (9.6 ± 2.2)	172 ± 38 (9.6 ± 2.1)	173 ± 43 (9.6 ± 2.4)	0.87
BG <70 mg/dL, *n* (%)	31 (14)	16 (15)	15 (14)	0.87
BG <54 mg/dL, *n* (%)	15 (7)	8 (7)	7 (7)	>0.99
BG <40 mg/dL, *n* (%)	0	0	0	N/A
BG 140–260 mg/dL, *n* (%)	116 (54)	59 (55)	57 (53)	0.89
BG >260 mg/dL, *n* (%)	87 (40)	45 (42)	42 (39)	0.72
BG >350 mg/dL, *n* (%)	5 (2)	4 (4)	1 (1)	0.37
Insulin dosage				
Total daily dose, units/day	44 ± 37	47 ± 43	41 ± 30	0.52
Total daily basal, units/day	30 ± 19	30 ± 20	30 ± 18	0.81
Total daily prandial, units/day	20 ± 18	20 ± 20	21 ± 16	0.30
Received SSI, *n* (%)	134	98 (91)	36 (34)	<0.0001
Total daily SSI, units/day	7 ± 4	7 ± 4	8 ± 4	0.34
Composite complications, *n* (%)	23 (11)	12 (11)	11 (10)	0.84
Acute kidney injury	21 (10)	10 (9)	11 (10)	0.82
Infection	1 (0)	0 (0)	1 (1)	0.52
Pneumonia	0	0	0	N/A
Death	1 (0)	1(1)	0 (0)	1.00

Data are means ± SD unless otherwise indicated. 70 mg/dL, 3.9 mmol/L; 54 mg/dL, 3.0 mmol/L; 40 mg/dL, 2.2 mmol/L; 140 mg/dL, 7.8 mmol/L; 260 mg/dL, 14.4 mmol/L; 350 mg/dL, 19.4 mmol/L. N/A, not applicable; SSI, supplemental sliding scale insulin.

minor differences in total daily insulin doses and basal insulin doses between the intensive and nonintensive supplement groups. The nonintensive supplement group received statistically higher doses of prandial insulin (19 ± 16 units/day) compared with the intensive group (14 ± 10 units/day, $P = 0.045$). Among the subjects who had any BG >260 mg/dL (14.4 mmol/L) with both groups receiving supplemental sliding scale insulin by protocol, there were no differences in mean daily BG or total daily, basal, prandial, or supplemental insulin. However, total insulin doses were higher in the subjects who had BG >260 mg/dL (14.4 mmol/L) compared with subjects with BG 140–260 mg/dL (7.8–14.4 mmol/L).

Table 3—Differences in glycemic control and insulin doses stratified by glucose levels

	Intensive	Nonintensive	*P*
BG between 140 and 260 mg/dL (7.8 and 14.4 mmol/L), no BG >260 mg/dL			
n	59	57	
Mean daily BG, mg/dL	163 ± 32	164 ± 30	0.65
Total daily insulin dose, units/day	33 ± 26	33 ± 27	0.75
Basal insulin, units/day	24 ± 15	26 ± 18	0.66
Prandial insulin, units/day	14 ± 10	19 ± 16	0.045
SSI, units/day	5 ± 2	N/A	N/A
At least one BG >260 mg/dL (>14.4 mmol/L)			
n	45	42	
Mean daily BG, mg/dL	190 ± 37	199 ± 43	0.57
Total daily insulin dose, units/day	64 ± 52	53 ± 31	0.48
Basal insulin, units/day	35 ± 24	33 ± 18	0.98
Prandial insulin, units/day	28 ± 26	24 ± 17	0.82
SSI, units/day	9 ± 4	8 ± 4	0.10

Data are mean ± SD unless otherwise indicated. N/A, not applicable; SSI, supplemental sliding scale insulin.

CONCLUSIONS

In this randomized controlled study we aimed to establish the safety and efficacy of the widely used practice of using supplemental rapid-acting insulin for correction of hyperglycemia in hospitalized patients with type 2 diabetes treated with basal-bolus regimen. The results of our study show that with active daily titration of basal-bolus insulin therapy, there is no added benefit for the use of supplemental/correction rapid-acting insulin in patients with BG 140–260 mg/dL. The use of a less aggressive supplemental insulin (BG >260 mg/dL [14.4 mmol/L]) resulted in noninferior glycemic control in comparison with a more aggressive supplemental insulin (BG >140 mg/dL [7.8 mmol/L]), which is the current standard of care. Despite a lower number of subjects in the nonintensive supplement group receiving supplemental insulin, there were no differences in glycemic control between the groups. Further, within the group of subjects with BG levels between 140 and 260 mg/dL (7.8 and 14.4 mmol/L), mean daily BG did not differ despite the nonintensive group not receiving any supplemental insulin. Results from this study challenge the current practice of using supplemental sliding

scale insulin with basal-bolus insulin treatment for patients with BG <260 mg/dL.

Extensive evidence has shown that inpatient hyperglycemia is associated with increased mortality, morbidity, length of stay, and cost (1,2,4,18). RCTs and observational studies show that treatment with basal-bolus insulin regimen is associated with improved outcomes (3,6,7) compared with sliding scale alone. Hence, international guidelines recommend a program with basal-bolus with the addition of supplemental sliding scale insulin before meals and bedtime. However, the basal-bolus with supplemental sliding scale insulin is based on treatment for type 1 diabetes and is underutilized (12–15). Electronic glucose management systems may increase compliance, but they are expensive and their use with subcutaneous insulin regimens is variable (19). Therefore, simplified basal-bolus regimens could help with compliance of using basal-bolus insulin regimens. We have shown that a less aggressive supplemental insulin regimen at bedtime for mild-to-moderate hyperglycemia does not change glycemic control in hospitalized patients with type 2 diabetes (16). Results from our current study show that using less aggressive supplemental sliding scale insulin during daytime did not change glycemic control for hospitalized patients with type 2 diabetes with BG < 260 mg/dL (14.4 mmol/L). The use of basal bolus with supplemental insulin is complex, requiring several dose calculations and increasing nursing and patient care burden, and is associated with frequent hypoglycemia (3,10). Given the lack of added benefit of supplemental rapid-acting insulin to basal-bolus regimens in patients with BG 140–260 mg/dL, adoption of a less aggressive supplemental insulin regimen while optimally titrating the basal-bolus insulin regimen has the potential to simplify and decrease errors in administering insulin treatment regimens in patients with mild/moderate hyperglycemia.

Of interest, subjects in both randomized groups received similar amounts of insulin for both basal and prandial insulin. There were also no differences in supplemental insulin doses between the intensive and nonintensive supplement groups. The lack of difference between the basal and prandial doses was likely due to active daily titration of basal and rapid-acting prandial insulin for hyperglycemia. Another reason for the lack of differences in supplemental insulin doses is the number of people with BG >260 mg/dL. According to the study protocol, both groups received the same supplemental insulin dose for BG >260 mg/dL. However, ~40% of subjects in both groups had BG >260 mg/dL. The amount of supplemental insulin in the nonintensive group can be explained by the subjects with BG >260 mg/dL needing an average of 8 units/day. Further, in the nonintensive group, only 36 subjects received supplemental insulin compared with 98 subjects in the intensive group. Among the subjects who received supplemental insulin, there were no differences in supplemental doses.

Our results add to the data from Basal Plus Trial (10) showing that treatment with basal once daily plus correction before meals resulted in glycemic control similar to that with a basal-bolus insulin regimen. The addition of supplemental treatment is needed in using basal insulin alone, but our study showed no additional benefits in patients receiving basal with prandial insulin. However, it should be noted that there are a few differences between the Basal Plus Trial and the current study. ~ 60% of the subjects included in the current study were on home insulin therapy with an average diabetes duration of 12 years (3,10,11). In comparison, our previous studies of inpatient diabetes had 30–40% of patients treated with home insulin therapy and the average duration of diabetes was 6–10 years (3,10,11). Specifically, in the Basal Plus Trial, the average duration of diabetes was 7.6 years with >60% of subjects with diabetes managed with oral antidiabetes medications at home. The subjects in this study had more poorly controlled diabetes as well as higher overall mean BG in the hospital compared with our previous studies (3,10,11). The higher glucose levels are consistent with our previous data showing that patients with higher admission BG and HbA_{1c} are less likely to have BG controlled in the hospital (20). Based on the results from the current study, for patients who have poorly controlled diabetes and need basal-bolus insulin therapy during hospitalization, a less aggressive regimen where supplemental insulin is initiated at a higher glucose threshold level results in noninferior BG levels.

Our study has several limitations. We excluded patients with type 1 diabetes, type 2 diabetes with marked hyperglycemia (BG > 400 mg/dL [22.2 mmol/L]), or ICU admission; patients on glucocorticoid therapy; and patients with significant chronic hepatic or renal disease. Although the optimal treatment regimen is not known, patients with type 1 diabetes and patients receiving glucocorticoid therapy may benefit from more intensive therapy, while patients with chronic hepatic and renal disease may need less intensive therapy. Optimal inpatient treatment of hyperglycemia in these special populations needs to be further studied. This cutoff was chosen for safety and to match the supplemental sliding scale used in our previous studies where supplemental insulin was given at 40 mg/dL increments (3,10,11,16). However, it is likely that a cutoff >250 mg/dL with increments of 50 mg/dL can be used to administer supplemental insulin. It is also possible that the intensive group would have fewer subjects with BG >260 mg/dL (14.4 mmol/L) due to receiving more aggressive supplemental insulin treatment. However, in our post hoc analysis (Table 3), similar numbers of subjects in the intensive and nonintensive supplement groups had BG >260 mg/dL (14.4 mmol/L). Continuous glucose monitoring has been validated in the inpatient setting (21) and would have allowed for frequent monitoring, measurement of glucose variability, and detection of more hypoglycemic episodes (22) with the different regimens used. However, continuous glucose monitoring is still not used widely and point of care testing still remains the standard of care for inpatient diabetes treatment.

In summary, our study shows that in hospitalized non-ICU patients with T2D, a less aggressive insulin supplementation can be used to treat moderate hyperglycemia(<260 mg/dL [14.4 mmol/L]). This simplified basal-bolus regimen is expected to lead to easier implementation of insulin treatment without compromising glycemic control.

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Author Contributions. P.V. wrote the protocol, provided study oversight, interpreted data, wrote the first draft of the manuscript, and critically edited the manuscript. S.C., R.J.G., M.A.U., F.J.P., G.M.D., M.F., and A.M. participated in the recruitment of study subjects, implemented the study protocol, and critically edited and contributed to the manuscript. L.P. provided input into the study design, analyzed data, and critically edited the manuscript. G.E.U. conceptualized the study, provided resources, interpreted data, and critically edited the manuscript. P.V. and G.E.U. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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