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SAFETY AND EFFICACY OF DDP4-INHIBITORS FOR THE MANAGEMENT OF HOSPITALIZED GENERAL MEDICINE AND SURGERY PATIENTS WITH TYPE 2 DIABETES

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Abstract

Objective: DPP4-inhibitors (DPP4-i) have been shown to be effective for the management of inpatient diabetes. We report pooled data from 3 prospective studies using DPP4-i in general medicine and surgery patients with type 2 diabetes (T2D).

Methods: We combined data from 3 randomized studies comparing DPP4-i alone or in combination with basal insulin or a basal bolus insulin regimen. Medicine (n = 266) and surgery (n = 319) patients admitted with a blood glucose (BG) between 140 and 400 mg/dL, treated with diet, oral agents, or low-dose insulin therapy were included. Patients received DPP4-i alone (n = 144), DPP4-i plus basal insulin (n = 158) or basal bolus regimen (n = 283). All groups received correctional doses with rapid-acting insulin for BG >140 mg/dL. The primary endpoint was differences in mean daily BG between groups. Secondary endpoints included differences in hypoglycemia and hospital complications.

Results: There were no differences in mean hospital daily BG among patients treated with DPP4-i alone (170 ± 37 mg/dL), DPP4-i plus basal (172 ± 42 mg/dL), or basal bolus (172 ± 43 mg/dL), $P = .94$; or in the percentage of BG readings within target of 70 to 180 mg/dL (63 ± 32%,

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60 ± 31%, and 64 ± 28%, respectively; $P = .42$). There were no differences in length of stay or complications, but hypoglycemia was less common with DPP4-i alone (2%) compared to DPP4-i plus basal (9%) and basal bolus (10%); $P = .004$.

Conclusion: Treatment with DPP4-i alone or in combination with basal insulin is effective and results in lower incidence of hypoglycemia compared to a basal bolus insulin re gimen in general medicine and surgery patients with T2D.

INTRODUCTION

Extensive data from observational and prospective randomized controlled trials in hospitalized patients have shown that hyperglycemia is associated with poor clinical outcomes such as increased length of hospital stay, hospital complications, and death (1–6). Improved glycemic control with insulin treatment has been shown to reduce the risk of complications, as well as short-and long-term mortality (7–10). Current practice guidelines recommend the use of basal bolus insulin therapy with long- or intermediate-acting insulin preparations in combination with short- or rapid-acting insulin analogs for the management of hyperglycemia in hospitalized patients with type 2 diabetes (T2D) (11,12). Despite these recommendations, inpatient glycemic control is usually poor and insulin therapy is not always prescribed (13). Reluctance to initiate insulin relates to the labor intensity of the treatment, which involves several insulin injections daily, frequent blood glucose (BG) monitoring, and fear of hypoglycemia. In fact, hypoglycemia has been reported in up to 32% of patients treated with basal-bolus insulin and has been independently associated with increased morbidity and mortality in hospitalized patients (14–17).

Hospital use of oral antidiabetic agents (OADs) has not been recommended in clinical guidelines (12) due to limited safety and efficacy data from randomized controlled trials. However, 4 recent randomized controlled trials have reported on the safety and efficacy of dipeptidyl peptidase 4-inhibitors (DPP4-i) in general medicine and surgical patients with T2D (18–21). The results of these studies have shown that the use of sitagliptin (18,19), linagliptin (20), and saxagliptin (21), alone or in combination with insulin, results in similar improvement in glycemic control and in lower rates of hypoglycemia compared to basal bolus insulin regimens. We present the results of a post hoc analysis of pooled data from 3 randomized multicenter clinical trials, to assess the efficacy and safety of treatment with DPP4-i or the combination of DPP4-i plus basal insulin compared to basal bolus insulin regimen (standard of care) in general medicine and surgery patients with T2D.

METHODS

Study Design and Population

We pooled data from 3 randomized, multicenter, open-label clinical trials (ClinicalTrials.gov Identifiers: NCT01378117, NCT01845831, NCT02004366), comparing the safety and efficacy of DPP4-i alone or in combination with basal insulin with a basal bolus insulin regimen. These studies followed a similar inclusion and exclusion criteria with differences in DPP4-i agents and study populations.

The Sita-Pilot (18) study enrolled 90 adult patients with type 2 diabetes treated with diet, oral agents, and total daily dose of insulin ≤0.4 units/kg/day. Patients were randomized to receive sitagliptin once daily (with dose adjusted as per kidney function) alone, or in combination with glargine insulin with a starting total daily dose of 0.25 units/kg/day; or to basal bolus insulin regimen with glargine once daily and lispro before meals. The Sita-Hospital study (19), recruited 279 medicine and surgery patients treated with diet alone, any combination of oral antidiabetic agents, or low-dose insulin therapy (≤0.6 units/kg/day) prior to admission and compared the safety and efficacy of sitagliptin plus basal insulin with a basal-bolus insulin regimen for the inpatient management of patients with T2D in general medicine and surgery. Patients were randomized to receive sitagliptin plus glargine once daily at a starting dose of 0.2 units/kg/day if their randomization BG was 140 to 200 mg/dL, or 0.25 units/kg/day if their BG was 200 to 400 mg/dL or a basal bolus regimen. The linagliptin-surgery study (20) enrolled 280 patients with outpatient treatment with diet, oral agents, or total daily dose of insulin ≤0.5 units/kg/day, and determined the efficacy and safety of linagliptin alone (5 mg daily) compared to a basal-bolus insulin regimen in hospitalized surgical patients with T2D.

In the 3 trials, patients on the basal-bolus regimen received an initial total daily dose of insulin of 0.4 units/kg if BG was between 140 to 200 mg/dL and 0.5 units/kg if randomization BG was between 200 to 400 mg/dL. Half the total insulin dose was given as glargine once daily and half as rapid-acting insulin divided in 3 equal doses before meals. Treatment target was to achieve and maintain a fasting and premeal BG concentration between 100 and 180 mg/dL. Patients in all 3 groups received supplemental correction doses of rapid-acting insulin before meals and bedtime for BG >140 mg/dL. BG was checked before each meal and at bedtime (or every 6 hours if a patient was not eating) using a point-of-care glucose meter. Furthermore, BG was measured at any time if a patient had symptoms of hypoglycemia or if requested by the treating physician. HbA1c was measured on admission. Treatment failure was defined as an average daily BG >240 mg/dL or 2 consecutive values BG >240 mg/dL. If failure occurred, participants were switched and treated similarly to those in the basal-bolus group.

These 3 studies followed a similar inclusion and exclusion criteria. Patients were included if they were aged 18 to 80 years old, had known history of T2D, were expected to stay in the hospital for more than 24 hours, had a BG prior to randomization between 140 and 400 mg/dL, and received outpatient treatment with diet, any combination of oral antidiabetic agents, or low-dose insulin therapy.

Patients were excluded if they were admitted to or expected to require intensive care unit, had a history of type 1 diabetes, had an unknown prior diagnosis of diabetes, had outpatient treatment with a DPP4-i or a glucagon-like peptide 1 receptor agonist, had a history of pancreatitis or active gallbladder disease, corticosteroid therapy, clinically relevant hepatic disease, or impaired renal function (glomerular filtration rate [GFR] <30 mL/min per 1.73 m^2 or serum creatinine >3.0 mg/dL) and also patients with a history of diabetic ketoacidosis, pregnancy, or any mental condition rendering the subject unable to give informed consent. In addition, in the 3 studies, we excluded patients with gastrointestinal obstruction or ileus

requiring gastrointestinal suction, and patients expected to be without oral intake for >48 hours.

Outcome Measures

The primary outcome was to determine differences in DPP4-i alone, DPP4-i plus glargine, and the basal-bolus group on glycemic control as measured by mean daily BG concentrations. Secondary outcomes were number of hypoglycemic episodes (<70 mg/dL, <54 mg/dL, and <40 mg/dL), number of BG values within range (70 to 180 mg/dL), total daily dose of basal, prandial and supplemental insulin, length of hospital stay, a composite of hospital complications, and number of treatment failures as defined above.

Statistical Analyses

This study included data from participants with BG available for at least 24 hours after receiving study medication. We excluded blood glucose values after the occurrence of treatment failure.

We compared categorical variables using a 2-sided Chi-square test or a Fisher exact test. We used nonparametric Kruskal-Wallis tests to compare continuous variables. We also conducted logistic regression to evaluate the effects of potential predictors for binary outcomes, including good glycemic control, defined as all blood glucoses between 70 and 180 mg/dL, and the incidence of hypoglycemia. *P* values <.05 are considered as statistically significant. The data analyses were performed with SAS 9.4 (SAS, Cary, North Carolina).

RESULTS

We included 640 patients with 283 patients admitted to general medicine and 357 patients to general surgery services. Patients were treated with DPP4-i alone (n = 164), DPP4-i plus basal (n = 167) or basal bolus (n = 309). We excluded 55 patients because of screening failure or short hospital stay less than 24 hours after randomization. Thus, 585 patients were included in the analysis (DPP4-i, n = 144; DPP4-i plus basal, n = 158; basal bolus, n = 283). Demographics and baseline characteristics are presented in Table 1. There were no differences between the treatment groups in age, gender, body mass index (BMI), body weight, or duration of diabetes. There were no differences in randomization BG between the groups; however, patients in the DPP4-i group had lower admission HbA1c compared to the DPP4-i plus glargine and the basal-bolus groups (Table 1).

Glycemic control data is shown in Table 2. All treatment regimens resulted in prompt and sustained improvement in mean daily BG concentration during the hospital stay (Fig. 1). The mean daily blood glucose concentration did not differ among the DPP4-i versus DPP4-i plus basal and the basal bolus groups (171 ± 39 mg/dL versus 171 ± 42 mg/dL versus 172 ± 45 mg/dL; $P = .95$). There were no differences between groups in the proportion of glucose readings within the blood glucose target between 70 and 180 mg/dL (63 ± 32% versus 60 ± 31% versus 64 ± 28%; $P = .42$) as well as in the proportion of treatment failures (17% versus 16% versus 14%; $P = .7$).

We performed additional analysis by stratifying patients according to randomization: BG <200 mg/dL or ≥200 mg/dL. Patients with BG <200 mg/dL at randomization had a lower mean daily BG (156 ± 32 mg/dL versus 193 ± 47 mg/dL; $P<.001$), a higher number of BGs within the target of 70 to 180 mg/dL (74 ± 24% versus 46 ± 30%; $P<.001$) and less percentage of treatment failures (9% versus 24%; $P<.001$) compared to patients with a randomization BG >200 mg/dL. However, there were no differences in the rates of hypoglycemia between groups (Table 2). Among patients with a randomization BG <200 mg/dL treated with DPP4-i alone, DPP4-i plus basal and basal bolus, the mean daily BG was 158.0 ± 34 mg/dL, 156.1 ± 33.6 mg/dL, and 155.7± 29.9 mg/dL, respectively ($P = .98$). In contrast, for patients with a BG ≥200 mg/dL treated with DPP4-i, DPP4-i plus basal and basal bolus, the mean daily BG was 196.5 ± 35.3 mg/dL, 189.3 ± 43.7 mg/dL, and 192.8 ± 52.0 mg/dL, respectively ($P = .27$) (Table 2).

The total daily insulin dose was significantly lower in the DPP4-i group compared with the other groups as expected (10 ± 8 units/day versus 26 ± 15 units/day versus 29 ± 17 units/day; $P<.001$). In addition, patients in the DPP4-i plus basal group received less supplemental insulin than those treated with DPP4-i only or basal bolus (DPP4-i: 10 ± 8 units/day versus DPP4-i plus basal: 5 ± 6 units/day versus basal-bolus:13 ± 9 units/day; $P<.001$).

Rates of hypoglycemia ≤70 mg/dL were significantly lower in the DPP4-i group compared to DPP4-i plus basal and basal bolus regimen (2% versus 9% versus 10%; $P = .004$). Few patients had a BG <54 mg/dL and <40 mg/dL, with no difference among the 3 groups, and only 1 patient had a BG ≤40 mg/dL.

In a multivariate model adjusting for hemoglobin A1c (HbA1c), age, gender, and BMI there were no differences in the odds of achieving good glycemic control (BG 70 to 180 mg/dL) between groups. The odds ratio (OR) for good glycemic control were 0.81 (95% confidence interval [CI] 0.43, 1.52) for basal-bolus and 0.86 (95% CI 0.41, 1.79) for DPP4-i + basal compared to DPP4-i alone. The odds for hypoglycemia were, however, significantly higher for basal bolus (OR 5.02, 95% CI 1.49, 16.94) and for DPP4-i + basal (OR 4.78, 95% CI 1.33, 17.25) compared to DPP-i alone.

DISCUSSION

This post-hoc analysis of pooled data from 3 prospective clinical trials showed that hospital treatment with DPP4-i alone or in combination with basal insulin resulted in a similar improvement in mean daily blood glucose concentration and the percentage of patients achieving glycemic targets compared to basal bolus insulin therapy in patients with T2D. In addition, treatment with DPP4-i alone was associated with fewer hypoglycemic events compared to the basal-bolus insulin group and DPP4-i plus basal insulin.

Recommendations from professional societies for the management of inpatient hyperglycemia have not been recently updated (5,12,22). Concerns were previously raised regarding potential adverse events with the use of older agents (i.e., metformin [lactic acidosis], sulfonylureas [sustained hypoglycemia], or thiazolidinediones [heart failure]). Despite such recommendations, older OADs are commonly used in the hospital; however,

no prospective studies have systematically evaluated these agents (23). In recent years, DPP4-i have consistently shown a safe profile in the outpatient setting (24–26). Similarly, our inpatient studies confirm the efficacy of this drug class in well-selected patients with uncontrolled hyperglycemia, and provide a safe therapeutic alternative with minimal risk of hypoglycemia. Furthermore, we did not observe any case of pancreatitis in patients exposed to DPP4-i. One patient randomized to basal bolus had a diagnosis of pancreatitis in the Sita-Hospital Trial (19).

Our results indicate that the efficacy of DPP4-i in improving and maintaining glycemic control relates to the randomization BG concentration. Patients with a randomization BG <200 mg/dL, had better glycemic control during the hospital stay compared to patients with a BG >200 mg/dL independent of their treatment assignment (Fig. 2). The number of BGs within target was significantly higher in patients with a randomization BG <200 mg/dL (74 ± 24% versus 46 ± 30%; P<.001) compared to those with a BG >200 mg/dL. Among patients with a BG <200 mg/dL, 74%, 70%, and 76% of patients treated with DPP4-i, DPP4-i plus basal, and basal bolus, respectively, maintained good glycemic control defined as a mean daily BG between 70 to 180 mg/dL. In contrast, a significant lower number of patients with a randomization BG ≥200 mg/dL maintained good glycemic control (40%, 47%, and 47% for DPP4-i, DPP4-i plus basal, and basal bolus regimen). In agreement with our analysis, Garg et al (21) recently reported that the use of saxagliptin, with supplemental rapid-acting insulin, showed similar efficacy in glycemic control when compared with basal-bolus insulin in non-critically ill hospitalized patients with T2DM treated prior to admission with <2 oral antidiabetic agents and with an admission BG <160 mg/dL. These results indicate that treatment with DPP4-i alone or in combination with basal insulin can be considered for the management of patients with mild- to moderate hyperglycemia.

There are several limitations including the open label design of the 3 clinical trials included in this pooled analysis. The results of this study do not apply to all patients admitted to the hospital with T2D as we excluded patients who were admitted to an intensive-care unit, with relevant hepatic disease, pancreatitis, an estimated GFR less than 30 mL/minute, severe hyperglycemia (>400 mg/dL), and patients receiving a total dose of insulin ≥0.6 units/kg per day before admission. In addition, statistical tests indicate similar baseline HbA1c between DPP4-i plus basal and basal bolus, but lower baseline HbA1c values in the DPP4-i group that could have resulted in a lower mean daily blood glucose concentration during the hospital stay in the DPP4-i group. However, the multivariate analysis adjusted for HbA1c, age, gender, and BMI, showed no differences in the odds of achieving good glycemic control between groups.

CONCLUSION

In summary, this post-hoc analysis supports the use of DPP4-i, alone or in combination with basal insulin in hospitalized patients with T2D who were treated at home with diet, any combination of oral antidiabetic drugs, or with low-dose insulin therapy. This treatment regimen resulted in a similar glycemic control with a lower daily insulin dose, fewer insulin injections, and a lower risk of hypoglycemia. Patients with mild to moderate hyperglycemia lower than 200 mg/dL are the best candidates to receive DPP4-i in the hospital. Patients

with higher BG levels >200 mg/dL may be treated with DPP4-i in combination with basal insulin or basal bolus insulin regimen. In addition, patients receiving high insulin doses prior to admission should also be treated with basal bolus insulin regimens.

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Authors' Contributions

GEU is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CLG and EAS wrote the first draft of the manuscript. DRU, PV, GMD, FJP, SC, MF, LP, and GEU reviewed/edited the manuscript and contributed to the discussion. LP conducted the statistical analysis.

Abbreviations:

BG	blood glucose
BMI	body mass index
CI	confidence interval
DPP4-i	dipeptidyl peptidase 4-inhibitors
HbA1c	hemoglobin A1c
OR	odds ratio
T2D	type 2 diabetes

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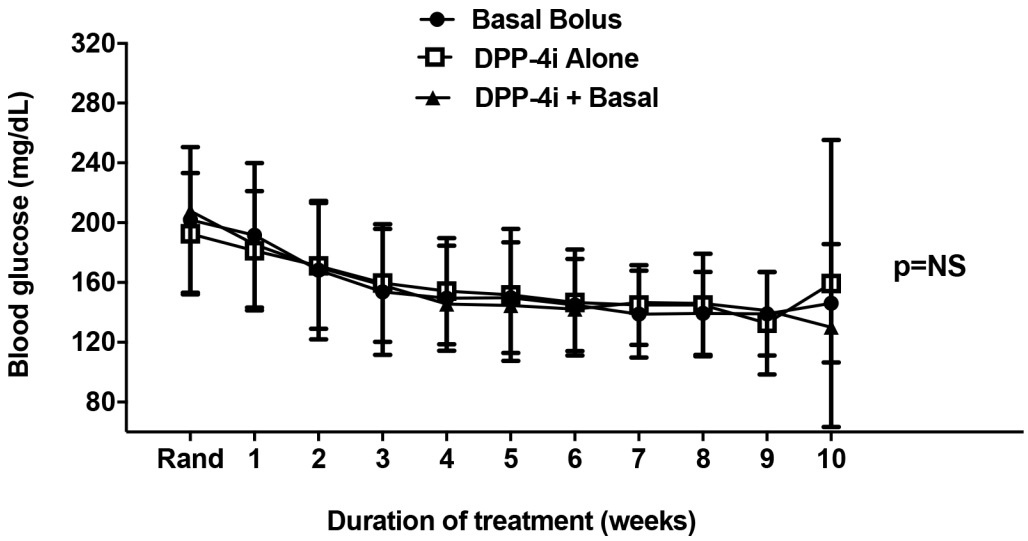

Fig. 1.

Differences in glycemic control in medicine and surgery patients with T2D treated with DPP4-i versus DPP4-i + basal insulin and basal bolus insulin. *DPP4-i* = dipeptidyl peptidase 4-inhibitors; *NS* = not significant; *Rand* = randomization; *T2D* = type 2 diabetes.

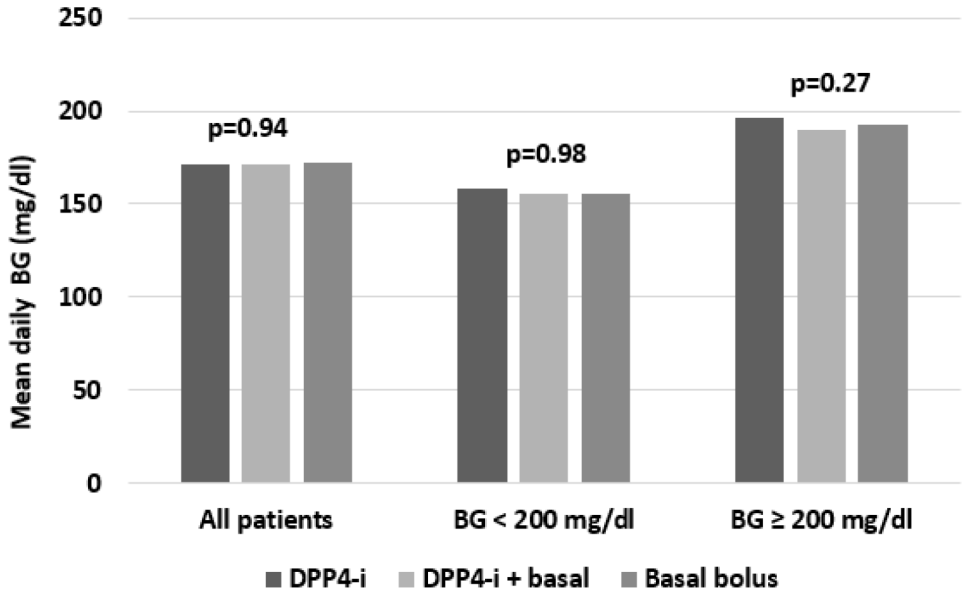

Fig. 2.

Mean daily BG levels during the study period in the DPP4-i, DPP4-i + basal, and basal bolus groups. When compared in the total number of patients, all treatment regimens resulted in a prompt and sustained improvement in mean daily BG concentration during the hospital stay. After stratifying by randomization for BG, we observed that patients with a randomization BG <200 mg/dL, had better glycemic control during the hospital stay compared to patients with a BG >200 mg/dL independent of their treatment assignment. *BG* = blood glucose; *DPP4-i* = dipeptidyl peptidase 4-inhibitors.

Table 1

Demographics and Baseline Characteristics

	DPP4-i	DPP4-i + basal	Basal-bolus	*P* value
Number of patients	144	158	283	
Sex				.27
Female, n (%)	73 (51%)	71 (45%)	120 (42%)	
Male, n (%)	71 (49%)	87 (55%)	163 (58%)	
Age, years	57.9 ± 10.8	57.3 ± 11.3	57.2 ± 11.0	.68
BMI, kg/m^2	35.4 ± 9.0	35.5 ± 10.6	33.6 ± 8.6	.08
Body weight, kg	102.2 ± 26.6	103.7 ± 32.8	99.2 ± 27.0	.44
Median duration of diabetes, years (IQR)	6.0 (3, 10)	9.0 (4, 15)	8.0 (4, 15)	.07
Length of stay, days, median (IQR)	4.0 (3, 6)	4.0 (3, 8)	4.0 (3, 7)	.12
HbA1c, %	7.6 ± 2.0	8.6 ± 2.4	8.3 ± 2.1	<.01
Randomization BG, mg/dL	193 ± 41	208 ± 53	202 ± 49	.07

Abbreviations: BG = blood glucose; BMI = body mass index; DPP4-I = dipeptidyl peptidase 4-inhibitors; HbA1c = hemoglobin A1c; IQR = interquartile range.

Table 2

Primary and Secondary Outcomes

	DPP-4i	DPP-4i + basal	Basal-bolus	*P* value
Number of patients	144	158	283	
Mean hospital daily BG, mg/dL	171 ± 39	171 ± 42	172 ± 45	.94
Treatment failure, n (%)	24 (17%)	25 (16%)	39 (14%)	.7
% BG within target, 70–180 mg/dL	63 ± 32	60 ± 31	64 ± 28.0	.42
BG <70 mg/dL, n (%)	3 (2%)	14 (9%)	29 (10%)	.004
BG <54 mg/dL, n (%)	1 (1%)	2 (1%)	2 (1%)	>.99
BG <40 mg/dL, n (%)	1 (1%)	0 (0%)	0 (0%)	.25
Total insulin dose, units/day	10 ± 8	26 ± 15	29 ± 17	<.001
Glargine, units/day	0.5 ± 2	21 ± 12	17 ± 10	<.001
Rapid-acting insulin, units/day	10 ± 8	5 ± 6	13 ± 9	<.001
Patients with randomization BG <200 mg/dL				
	DPP4-i	**DPP4-i + basal**	**Basal-bolus**	***P* value**
Mean daily BG, mg/dL	158 ± 35	156 ± 34	156 ± 30	.98
Treatment failure, n (%)	10 (10%)	6 (8%)	13 (8%)	.79
% BG within target, 70–180 mg/dL	74 ± 27	70 ± 26	76 ± 20	.29
BG <70 mg/dL, n (%)	2 (2%)	8 (10%)	18 (11%)	.018
BG <54 mg/dL, n (%)	1 (1%)	1 (1%)	1 (1%)	1
BG <40 mg/dL, n (%)	1 (0%)	0 (0%)	0 (0%)	.53
Total insulin dose, units/day	8 ± 6	22 ± 12	24 ± 12	<.001
Glargine, units/day	1 ± 3	18 ± 11	13 ± 8	<.001
Rapid-acting insulin, units/day	8 ± 6	4 ± 4	10 ± 8	<.001
Patients with randomization BG ≥200 mg/dL				
	DPP4-i	**DPP4-i + basal**	**Basal-bolus**	***P* value**
Mean daily BG, mg/dL	196 ± 35	190 ± 44	193 ± 52.0	.27
Treatment failure, n (%)	14 (30%)	18 (25%)	26 (22%)	.54
% BG within target, 70–180 mg/dL	40 ± 30	47 ± 31	47 ± 29	.29
BG <70 mg/dL, n (%)	1 (2%)	5 (7%)	11 (9%)	.3
BG <54 mg/dL, n (%)	0 (0%)	1 (1%)	2 (2%)	1
BG <40 mg/dL, n (%)	0 (0%)	0 (0%)	0 (0%)	-
Total insulin dose, units/day	14 ± 9	30 ± 16	37 ± 18	<.001
Glargine, units/day	0.1 ± 0.6	24 ± 13	21 ± 11	<.001
Rapid-acting insulin, units/day	13 ± 9	7 ± 6	16 ± 10	<.001

Abbreviations: BG = blood glucose; DPP4-i = dipeptidyl peptidase 4-inhibitors. Treatment failure was defined as an average daily BG >240 mg/dL, or 2 consecutive values of BG >240 mg/dL.