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A Randomized Controlled Study Comparing a DPP4 Inhibitor (Linagliptin) and Basal Insulin (Glargine) in Patients With Type 2 Diabetes in Long-term Care and Skilled Nursing Facilities: Linagliptin-LTC Trial

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Abstract

Objectives—Safe and easily implemented treatment regimens are needed for the management of patients with type 2 diabetes mellitus (T2DM) in long-term care (LTC) and skilled nursing facilities.

Design—This 6-month open-label randomized controlled trial compared the efficacy and safety of a DPP4 inhibitor (linagliptin) and basal insulin (glargine) in LTC residents with T2DM.

Settings—Three LTC institutions affiliated with a community safety-net hospital, US Department of Veterans Affairs and Emory Healthcare System in Atlanta, Georgia.

Participants—A total of 140 residents with T2DM treated with oral antidiabetic agents or low-dose insulin (0.1 U/kg/d), with fasting or premeal blood glucose (BG) > 180 mg/dL and/or HbA1c > 7.5%.

Intervention—Baseline antidiabetic therapy, except metformin, was discontinued on trial entry. Residents were treated with linagliptin 5 mg/d (n = 67) or glargine at a starting dose of 0.1 U/kg/d (n = 73). Both groups received supplemental rapid-acting insulin before meals for BG > 200 mg/dL.

Measurements—Primary outcome was mean difference in daily BG between groups. Main secondary endpoints included differences in frequency of hypoglycemia, glycosylated hemoglobin (HbA1c), complications, emergency department visits, and hospital transfers.

Results—Treatment with linagliptin resulted in no significant differences in mean daily BG (146±34 mg/dL vs. 157±36 mg/dL, *P* = .07) compared to glargine. Linagliptin treatment resulted

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in fewer mild hypoglycemic events <70 mg/dL (3% vs. 37%, $P < .001$), but there were no differences in BG < 54 mg/dL ($P = .06$) or <40 mg/dL ($P = .05$) compared to glargine. There were no significant between-group differences in HbA1c, length of stay, complications, emergency department visits, or hospitalizations.

Conclusion—Treatment with linagliptin resulted in noninferior glycemic control and in significantly lower risk of hypoglycemia compared to insulin glargine in long-term care and skilled nursing facility residents with type 2 diabetes.

Keywords

Incretin; DPP4 inhibitors; long-term care; nursing home; skilled nursing facilities; glargine; linagliptin; basal insulin; hospital hyperglycemia; older adults; diabetes

Diabetes mellitus is highly prevalent in the elderly, afflicting ~25% of older adults aged 65-75 years and ~40% of adults older than 80 years of age.¹ Between 2001 and 2010, the percentage of people with diabetes increased by 127% (9.1%-20.7%) for those aged 65-74 years, and 126% (8.9%-20.1%) for those aged 75 years and older.² The prevalence of diabetes in long-term care (LTC) facilities is reported between 15% and 34%.³⁻⁶ Most patients in LTC facilities are treated with oral antidiabetic drugs (OADs) in combination with sliding scale regular insulin or with basal bolus insulin regimen,⁷ with a reported prevalence of hypoglycemia of ~28% to 40%.⁷⁻⁹ Residents with hypoglycemia have a longer length of stay, more emergency department or hospital transfers, and higher mortality compared to those without hypoglycemia.⁷ In a recent study in LTC residents with T2DM, we randomized 150 patients with diabetes to receive low-dose basal or to continue OADs for 26 weeks.⁸ We reported a similar improvement in HbA1c and a frequency of hypoglycemia observed in 27% of patients receiving basal insulin and 31% in the OAD group.⁸ These results indicated the need for investigating safe, effective, and easily implemented protocols to achieve glucose control with a low rate of hypoglycemia in this vulnerable population.

The overall objective of this study was to investigate if treatment strategies shown effective in improving glucose control with low rates of hypoglycemia in the hospital could be meaningfully translated to the LTC setting.¹⁰⁻¹³ Management of diabetes in LTC is often more complex than implementing treatment strategies for hospital care. In LTC, there are fewer provider and nursing resources, and although the LTC population is heterogeneous, there is a preponderance of older, more vulnerable patients with compromised functional and cognitive status along with significant comorbidities that may need different treatment strategies.^{14,15} Accordingly, we compared a low-dose basal insulin protocol¹⁰ and the use of dipeptidyl peptidase-4 (DPP4) inhibitor, which have recently been shown to be safe and effective in hospitalized patients with T2DM.^{12,13} The central hypothesis was that treatment with linagliptin, a once-daily oral DPP4-inhibitor, results in similar improvement in glucose control but in a lower rate of hypoglycemia compared to basal insulin in LTC residents with T2DM.

Methods

Design Overview

This randomized open-label study included LTC facility residents with a known history of T2DM admitted to 3 LTC institutions in an urban setting, one affiliated with a safety-net hospital, one operated by an academic medical health system, and one US Department of Veterans Affairs community-living center in Atlanta, Georgia. Individuals admitted for long-term stay, subacute rehabilitation, or postacute stays were included in the study. The institutional review board at Emory University approved the study protocol, and the trial was registered at ClinicalTrials.gov, number NCT02061969.

Participants and Recruitment

After identification of eligible residents, research staff obtained informed consent from the participant or legal representative. We included male and female residents with known history of T2DM, BG > 180 mg/dL, and/or with HbA1c >7.5% while receiving treatment with diet, OADs as monotherapy or in combination therapy, or with insulin at a total daily dose 0.1 U/kg. We excluded subjects with a history of type 1 diabetes or with a history of diabetic ketoacidosis,¹⁶ previous treatment with insulin at a dose >0.1 U/kg/d, DPP4-inhibitors or glucagon-like peptide receptor analogs (GLP1-RA) use during the past 3 months prior to admission, as well as residents with severe or recurrent hypoglycemic events, history of gastrointestinal obstruction or gastroparesis, acute or chronic pancreatitis or pancreatic cancer, clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease, portal hypertension), elevated alanine aminotransferase and aspartate aminotransferase >3 times upper limit of normal, impaired renal function (glomerular filtration rate < 45 mL/min), corticosteroids and immunosuppressive treatment, or with mental condition rendering the subject unable to understand the nature and scope of the study.

Randomization and Intervention

An independent statistician provided a computer-generated randomization list for each institution. Participants were randomized via parallel design to either basal insulin or linagliptin therapy in a 1:1 ratio.

Treatment Groups

Oral antidiabetic drugs (except metformin, if no contraindication) and insulin were discontinued on trial entry. Participants in the glargine group were started at an insulin dose of 0.1 U/kg administered once daily at the same time of the day. The total daily insulin dose was adjusted to a fasting and pre-meal glucose target between 100 and 180 mg/dL (Appendix Table 1, treatment protocol). The total daily dose of insulin was increased by 10% every 3 to 5 days for fasting BG between 181 and 280 mg/dL, and by 20% for fasting BG > 280 mg/dL. The dose was maintained if glucose levels remained between 100 and 180 mg/dL. The dose of insulin was reduced by 10% for fasting or premeal blood glucose (BG) between 70 and 99 mg/dL, by 20% for fasting or premeal BG between 41 and 69 mg/dL, and by 40% for glucose <40 mg/dL. Residents in the linagliptin group received a single

daily dose of 5 mg once daily. Supplemental insulin with rapid-acting insulin (lispro insulin) was given before meals for glucose >200 mg/dL per sliding scale (see Appendix Table 1 for details).

Capillary BGs was ordered before each meal and bedtime using a glucose meter. Additional BGs were measured if subjects had symptoms of hypoglycemia or if primary team deems it necessary.

Outcomes and Follow-up

The primary outcome of the study was to compare the overall mean daily BGs between the groups. Secondary outcomes were number of hypoglycemic events (<70, <54, and <40 mg/dL), glycosylated hemoglobin (HbA1c), mean fasting BG concentration, infections, cardiac complications including myocardial infarction, cardiac arrhythmia and heart failure, acute kidney injury defined as an increment >0.5 mg/dL in serum creatinine from baseline, and mortality (death occurring during LTC admission). We also registered frequency in emergency department visits or hospitalizations and mortality during the study period. Treatment failure was arbitrarily defined as 3 consecutive glucose values > 280 mg/dL or a mean daily glucose >280 mg/dL.^{8,10} In addition, we explored differences in the amplitude of blood glucose excursions or glycemic variability—a marker of inpatient clinical outcome—between residents treated with glargine and linagliptin.^{17–19}

Research coordinators entered baseline and daily research information into data collection paper forms and into a HIPAA (Health Insurance Portability and Accountability Act of 1996)–compliant and secure electronic database (REDCap) provided by the Emory Research Information Technology Department. Baseline data included demographics/history form (subject gender, age, ethnicity, type of treatment, and comorbid conditions, body weight, and body mass index). Daily information was collected on treatment, blood glucose and laboratory values, hospital complications, and adverse events. We also collected information on a composite of acute complications, including newly diagnosed infections, cardiac complications, and acute kidney injury. Nosocomial infections were diagnosed based on standardized Centers for Disease Control and Prevention criteria.²⁰ New infections were adjudicated if they occurred at least 48 hours after study initiation. Cerebrovascular accident was defined as neurologic deficit persisting >72 hours, transient ischemic attack, deficit resolving within 24 hours, or deficit lasting 24 to 72 hours (reversible ischemic neurologic deficit). Cardiovascular complications were defined per the standards of the American College of Cardiology–American Heart Association.²¹ We also registered frequency in emergency department visits or hospitalizations and mortality during the study period.

Statistical Analysis

This study was a randomized, open-label controlled trial. The primary endpoint of the study was noninferiority for differences between treatment groups on glycemic control determined by mean daily blood glucose concentrations. We defined noninferiority for the primary endpoint of mean blood glucose as a difference <18 mg/dL (1 mmol/L) with linagliptin versus basal insulin. A blood glucose difference of such a magnitude has been reported as nonclinically significant in the hospital setting, and is smaller than significant treatment

effects in other superiority trials.^{10,22,23} Based on our preliminary data in LTC,⁸ we assumed that a standard deviation of 40 mg/dL change is bounded above by 1%. With a 1-sided 2-sample *t* test, alpha = 0.05, with Bonferroni correction applied to adjust for multiple comparisons across different days on therapy, and after adjusting for 10% to 15% attrition, a total of 64 patients were required for both the linagliptin and the basal group to ensure 80% power to reject the noninferiority hypothesis. This led to a final total sample size estimate of 140 participants.

Main secondary endpoints included differences in the frequency of hypoglycemia, fasting glucose, HbA1c at 3 and 6 months of intervention, complications, emergency department visits, and hospitalizations. We made the comparisons using nonparametric Wilcoxon tests for continuous variables and χ^2 tests (or Fisher exact test) for discrete variables. We summarize demographics, baseline clinical characteristics, and clinical outcomes by the 2 treatment groups. Data are presented as mean $\pm$ standard deviation for continuous variables and present count (percentage) for categorical variables. The data are presented as mean (SD) for continuous variables and count (percentage) for discrete variables unless specified otherwise. We performed statistical analyses with SAS, version 9.3.

Results

Between February 2013 and October 2016, we assessed 211 residents for eligibility at 3 long-term care facilities (Appendix). Of these, 64 residents refused to participate, 5 patients were screen failures, and 2 subjects withdrew consent before receiving study medication. A total of 140 residents completed enrollment and randomization: 67 were assigned to linagliptin and 73 were assigned to basal insulin therapy with glargine insulin. The clinical characteristics of study participants are shown in Table 1. Groups were well matched without significant differences in mean age, gender, racial distribution, BMI, duration of diabetes, and comorbidities. A total of 117 (84%) were admitted to subacute rehabilitation services or postacute care and 23 patients (16%) were admitted for long-term care without difference between groups. The overall LTC stay was 48.9 ± 50 days, with no differences in length of stay between groups. At baseline, a total of 26 participants (19%) were on no pharmacologic therapy, 92 participants were on OADs alone (66%), 17 (12%) on insulin, and 5 participants (4%) were on a combination of OADs and insulin therapy. A higher number of patients in the linagliptin group were treated with OAD (75% vs. 58%), and fewer patients were treated with insulin alone or in combination with OADs (6% vs. 25%) compared to the basal insulin group. A total of 83 participants were treated with metformin: 41 participants in the glargine group (56%) and 42 participants (63%) in the linagliptin group during the LTC stay.

There was no difference on randomization BG concentration (231 ± 53 mg/dL vs. 233 ± 54 mg/dL, $P = .87$) between participants in the glargine and linagliptin groups. Both treatment regimens resulted in a sustained improvement in mean daily glucose concentration during the LTC stay (Figure 1A). Mean fasting BG during therapy was not significantly different between basal insulin and linagliptin groups (136.4 ± 35 mg/dL vs. 131.2 ± 27 mg/dL, $P = .55$). The overall mean daily BG level was lower in participants treated with linagliptin (146

± 34 mg/dL vs. 157 ± 36 mg/dL); however, this difference was not statistically significant, $P = .07$.

A total of 83 participants (59.3%) continued to receive metformin therapy, with similar number of participants in the linagliptin (42) and glargine group (41). There were no differences in the mean daily glucose in patients treated with glargine and metformin (152.2 ± 36 mg/dL) compared to linagliptin and metformin (141.4 ± 33 mg/dL) during the LTC stay, $P = .13$. The randomization HbA1c was $7.82\% \pm 2.2\%$ and $7.92\% \pm 2.2\%$ ($P = .74$) in the glargine and linagliptin groups. Both treatment regimens resulted in a significant improvement in glycemic control during LTC stay (Figure 1B).

The total daily insulin dose in the glargine and linagliptin groups was 0.15 ± 0.14 U/kg/d and 0.04 ± 0.02 U/kg/d, respectively, $P = .004$. The mean dose of glargine insulin was 10.6 ± 7.4 U/d (Table 2). There was no difference in the amount of supplemental insulin between the basal and linagliptin groups (6.9 ± 4.7 vs. 4.0 ± 1.7 U/d, $P = .22$).

Treatment with linagliptin was associated with an overall lower number of hypoglycemic events compared to basal insulin therapy (Figure 2, Table 2). Of the 73 participants in the insulin group, 27 (37%) had 136 events of BG < 70 mg/dL, 5 (7%) had a BG < 54 mg/dL, and 2 (3%) had 3 episodes of BG < 40 mg/dL. Two participants (3%) in the linagliptin group had 3 events of BG < 70 mg/dL (a 97% relative risk reduction compared to glargine) and no participants had a BG < 54 mg/dL ($P < .06$) or < 40 mg/dL ($P = .5$). The weekly average number of hypoglycemic events (BG < 70 mg/dL) was 0.19 ± 0.4 in the glargine and 0.00 ± 0.02 in the linagliptin group, $P < .001$. Glycemic variability was significantly lower in the linagliptin compared to the glargine group. Clinical characteristics of residents, with and without hypoglycemia, in the linagliptin and basal insulin group are shown in Appendix Table 2.

The rate of complications including infections, cardiovascular disease, acute kidney injury, emergency department visits, and hospital admissions were similar between groups (Table 2). There was no difference in mortality between groups. In addition, there was no difference in the frequency of treatment failure, ($P = .10$). There is no difference in treatment failures between groups ($P = .28$) even after correcting for randomization blood glucose cutoffs of 200 mg/dL.

Discussion

We report the results of the first randomized controlled trial comparing the safety and efficacy of a DPP4-inhibitor ($\pm$ metformin) and basal insulin glargine ($\pm$ metformin) in residents with T2DM admitted to LTC facilities. Our study indicates that treatment with linagliptin and basal insulin results in equivalent glycemic control without significant differences in mean daily and fasting blood glucose or in HbA1c concentration during LTC stay. Treatment with basal insulin was associated with higher numbers of hypoglycemic events compared to linagliptin therapy.

The burden of diabetes in the elderly and in LTC facilities is well established.^{9,24}) Residents with diabetes have greater incidence of hypertension, cardiovascular disease, depression,

heart failure, cerebrovascular events, kidney disease, visual impairment, and foot problems (including amputations),^{9,24–27} and have longer lengths of stay and mortality compared to residents without diabetes.

In agreement with previous studies, our results indicate that glycemic control in elderly LTC residents with diabetes is more often tight than poor.^{28,29} The average HbA1C levels reported in observational and randomized controlled studies in LTC have ranged between 5.9% and 7.5%,^{8,29} with HbA1C goals achieved in more than three-fourths of nursing home patients.³⁰ In the present study, the average HbA1c was $7.88 \pm 2.2\%$, and declined similarly in both treatment groups. Clinical guidelines and position statements have released target treatment recommendations for the management of patients with diabetes in LTC settings.^{1,31,32} An individualized approach with HbA1c goals was adapted based on frailty, life expectancy, comorbidities, cognitive and functional status, and available resources and support system. The HbA1C goal of $<7.5\%$ is recommended for residents with good cognitive and functional status and without significant hypoglycemia. A higher target may be appropriate in residents with a history of severe hypoglycemia, limited life expectancy, comorbid conditions and longstanding diabetic complications.³² In addition to individualized glycemic goals, appropriate selection of pharmacologic agents is needed to reduce the risk of hypoglycemia and adverse events. The American Geriatric Society Guidelines³³ recommends the use of metformin, unless contraindicated, as the preferred first-line agent in combination with lifestyle therapy. The American Medical Directors Association³⁴ and the American Diabetes Association for the management of diabetes in LTC and skilled nursing facilities³¹ have nonspecific recommendations with regard to choice of glucose-lowering agents, but advise practitioners to select simplified regimens with agents associated with low risk of hypoglycemia, and to avoid the use of sliding scale insulin as the single regimen of therapy.

Hypoglycemia is a common complication of diabetic therapy and the main limiting factor in achieving glycemic control in LTC and transitional care facilities.^{8,9,35} Hypoglycemia in elderly patients has been associated with increased risk of complications and mortality.^{7,36,37} In an observational study in 1409 LTC residents with T2DM, we reported that 42% of patients had at least 1 episode of hypoglycemia and patients with hypoglycemia were more likely to require emergency department care, hospital transfers, and had higher mortality than patients without hypoglycemia.⁷ A recent randomized controlled trial comparing treatment with oral agents and basal insulin, we recently reported a prevalence of hypoglycemia in 27% of patients treated with basal insulin and 31% of elderly patients treated with oral antidiabetic agents.⁸ In addition, in recent study using continuous glucose monitoring,³⁵ 65% of adults aged >69 years had at least 1 episode of hypoglycemia over a 3-day period, most of them were unrecognized by fingerstick monitoring or by symptoms. In the present study, despite the low starting insulin dose of 0.1 U/kg/d and an average total daily dose of 0.15 unit/kg/d, basal insulin therapy resulted in a higher rate of mild hypoglycemia <70 mg/dL (37% vs. 3%, $P < .001$), and in a nonsignificant trend in the number of patients with BG < 54 mg/dL (7% vs. 0%, $P = .06$) or BG < 40 mg/dL (3% vs. 0%, $P = .05$) compared to glargine. Multiple factors increase the risk of hypoglycemia in older adults, including variable appetite and nutritional intake, impaired renal function, polypharmacy, and slowed hormonal regulation and counterregulation.^{8,9}

Treatment with DPP4 inhibitors has been shown to be safe and effective for the inpatient management of selected general medicine and surgery patients with T2DM.^{11,12,38} Several randomized controlled trials have shown that in hospitalized patients with mild to moderate hyperglycemia, the use of once-daily DPP4 inhibitors results in similar mean daily blood glucose concentration with lower frequency of hypoglycemia compared to basal or basal bolus insulin regimen.^{11,39} Similarly, analysis of data pooled from individuals aged 65 years of placebo-controlled clinical trials of linagliptin in 841 subjects treated with linagliptin versus 490 who received placebo reported that linagliptin resulted in a reduction in HbA1c of ~0.7%, with low rate of hypoglycemia, and safety and tolerability similar to placebo in elderly patients with T2DM.⁴⁰ In agreement with these studies, this study indicates that the use of linagliptin is as effective as basal insulin in improving glycemic control with lower hypoglycemia risk in LTC residents with T2DM. These results suggest that an initial treatment with DPP4 inhibitors should be considered over basal insulin for the management of patients with T2DM in LTC settings. Future studies should determine if the low risk of hypoglycemia with DPP4 inhibitor therapy will safely allow for reductions in the frequency of BG testing, which may reduce costs and relieve time demands on the nursing staff in LTC facilities.

Increasing evidence indicates that glycemic variability is a strong predictor of clinical outcome and mortality, independent of absolute glucose concentration and severity of illness in hospitalized patients.^{17–19} Increased glucose variability is independently associated with longer length of stay and mortality in ICU and non-ICU patients; however, there is little information on the effect of glycemic variability in LTC settings. Our analysis indicates that treatment with linagliptin produced significant lower values of glycemic variability compared to insulin in LTC residents. In our study, higher glycemic variability was associated with increased risk of hypoglycemia in LTC residents with T2DM.

We acknowledge several limitations including a relatively small number of participants from a single geographic area, though from multiple LTC facilities. Because of limited resources, an evaluation of changes in cognitive function by Mini-Mental Examination was not performed as initially planned. We excluded participants with clinically relevant renal and hepatic disease, and pancreatitis. In such participants, insulin regimen may be preferred for achieving glycemic control. A higher number of patients in the linagliptin group were treated with OAD and fewer patients were treated with insulin prior to randomization compared to the insulin group, which may have resulted in differences in glycemic control and hypoglycemia. Block randomization with insulin use as a factor should be done in future studies to ensure equal treatment distribution. In addition, we recruited participants on oral agents and/or low-dose insulin therapy at a total dose of insulin 0.1 U/kg per day prior to randomization. Future studies should include insulin resistant LTC residents receiving higher insulin doses. Finally, most patients were admitted to subacute rehabilitation, thus future studies should focus on participants with diabetes admitted for long-term care.

Conclusion

The results of this randomized controlled trial indicate that elderly residents in LTC and skilled nursing facilities can achieve and maintain similar glycemic control, when treated

with linagliptin compared to basal insulin. Insulin therapy remains a useful agent for many elderly LTC residents, especially those with symptomatic hyperglycemia, history of hyperglycemic emergency, and those who fail to maintain glucose control with oral agents; however, the high rate of hypoglycemia represents a major limitation in LTC settings. Our results indicate that an initial treatment with a DPP4 inhibitor ($\pm$ metformin) has distinct safety advantages and comparable efficacy to insulin therapy to be considered as a first-line agent for most LTC residents with type 2 diabetes.

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Some data from this trial were presented orally at the 2017 American Diabetes Association meeting (San Diego, CA) in June 2017.

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Appendix

Study Flow Diagram.

Appendix Table 1

Treatment Protocol

1 Linagliptin Group

- Discontinue oral antidiabetic drugs (except metformin if no contraindication), insulin and non-insulin injected antidiabetic medication on admission.
- Start linagliptin 5 mg once daily
- **Supplemental (correction) insulin.** Supplemental (lispro, aspart) insulin will be administered before meals following the “supplemental” protocol for glucose >200 mg/dL.
 - If a patient is able and expected to eat all or most of his or her meals, supplemental insulin will be administered before or with each meal following the “usual” column dose.
 - If a patient is not able to eat, supplemental (lispro or aspart) insulin will be administered every 6 hours (6-12-6-12) following the “sensitive” dose of the sliding scale.

2 Glargine Insulin

- Discontinue oral antidiabetic drugs (except metformin if no contraindication), insulin and non-insulin injected antidiabetic medication on admission.
- Starting total daily insulin dose: 0.1 units per kg once daily at the same time of the day.
- **Insulin adjustment.** The total daily insulin dose will be adjusted as follows:
 - Fasting and pre-meal BG between <180 mg/dL without hypoglycemia the previous day: no change
 - Mean fasting BG between 181 and 280 mg/dL without hypoglycemia: increase glargine dose by 10% every 3 days
 - Mean fasting BG > 281 mg/dL without hypoglycemia: increase glargine dose by 20% every 3 days
 - Mean fasting BG between <100 mg/dL: decrease glargine dose by 10% everyday
 - If a patient develops hypoglycemia (<70 mg/dL), decrease glargine dose by 20%.
 - If a patient develops hypoglycemia (<40 mg/dL), decrease glargine dose by 40%.
- **Supplemental insulin.** Supplemental insulin will be administered following the “supplemental” protocol for BG > 200 mg/dL.
 - If a patient is able and expected to eat most of his/her meals, supplemental insulin will be administered before meals following the “usual” dose of the sliding scale protocol.
 - If a patient is not able to eat, supplemental insulin will be administered every 6 hours following the “usual” dose of the sliding scale protocol.

Supplemental insulin before meals

Blood Glucose (mg/dL)	Usual*	Insulin Resistant*
200	0	0
201-250	2	4
251-300	3	5
301-350	4	6
>351	5	8

* Check appropriate column below and cross out other columns. The numbers in each column indicate the number of units of lispro or aspart insulin per dose to be given before meals. Patients with persistent hyperglycemia could be moved to “insulin resistant” column.

Appendix Table 2**Characteristics of Participants With Hypoglycemia**

Variable	No Hypoglycemia (n = 111)	Hypoglycemia (n = 29)	P Value
Age, years	69.63 ± 13.6	70.41 ± 12.9	.93
BMI	30.77 ± 7.4	26.27 ± 5.5	.003
Body weight, kg	87.92 ± 22.2	74.86 ± 15.7	.005
Length of stay, days	40.53 ± 42.5	80.76 ± 61.3	<.001
Complications, n (%)			
Cardiovascular	1 (1)	0 (0)	1.00
Stroke	0 (0)	0 (0)	
Infections	9 (8)	5 (17)	.17
Acute kidney injury	2 (2)	1 (3)	.50
Mortality	2 (2)	0 (0)	1.00
Emergency department/hospital admission, n (%)			.49
Emergency department visit	2 (15)	1 (33)	
Hospital admission	11 (85)	2 (67)	
Mean daily insulin, U/kg/d	0.11 ± 0.08	0.21 ± 0.18	.09
Admission serum creatinine, mg/dL	1.02 ± 0.30	0.90 ± 0.26	.20
Glomerular filtration rate, mL/min	62.28 ± 10.2	62.00 ± 7.4	.98

Data are mean ± standard deviation.

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Fig. 1. Change in glycemic control in participants treated with glargine ($\pm$ metformin) and linagliptin ($\pm$ metformin) during the study period. (A) BG and duration of treatment; (B) HbA1c change at 3 and 6 months.

Fig. 2.
Frequency of hypoglycemia in participants treated with basal insulin ($\pm$ metformin) and linagliptin ($\pm$ metformin).

Table 1

Clinical Characteristics of Study Participants

Variable	All	Basal Insulin	Linagliptin	P Value
Number of participants	140	73	67	
Gender, n (%)				.10
Male	57 (41)	25 (34)	32 (48)	
Female	83 (59)	48 (66)	35 (52)	
Race, n (%)				.39
Black	84 (60)	42 (58)	42 (63)	
White	52 (37)	30 (41)	22 (33)	
Other	4 (3)	1 (1)	3 (4)	
Age, years	69.8 ± 13	71.5 ± 13	68 ± 14	.19
BMI	29.9 ± 7.3	30.0 ± 8	29.7 ± 7.0	.97
Body weight, kg	85.2 ± 22	83.7 ± 20	86.9 ± 23	.48
Duration diabetes, years	10.7 ± 9	10.6 ± 9	10.9 ± 9	.78
Admission service, n (%)				1.00
Long-term care	23 (16)	12 (16)	11 (16)	
Subacute rehabilitation	117 (84)	61 (84)	56 (84)	
Length of stay, days	48.9 ± 50	48.9 ± 50	48.8 ± 50	.89
Admission diabetes therapy, n (%)				.014
Diet alone	26 (19)	13 (18)	13 (19)	
Oral antidiabetic agents	92 (66)	42 (58)	50 (75)	
Insulin alone	17 (12)	13 (18)	4 (6)	
Insulin and oral agents	5 (4)	5 (7)	0 (0)	
Hypertension, n (%)	108 (77)	52 (71)	56 (84)	.08
Heart failure, n (%)	7 (5)	5 (7)	2 (3)	.44
Dyslipidemia, n (%)	66 (47)	34 (47)	32 (48)	.89
Dementia, n (%)	6 (4)	5 (7)	1 (1)	.21

Data are mean ± standard deviation unless otherwise noted.

Table 2

Glycemic Control, Insulin Therapy, Hypoglycemia, Glycemic Variability, and Complications in LTC Residents Treated With Basal Insulin and Linagliptin Therapy

	All	Glargine	Linagliptin	P Value
Glycemic control				
Randomization BG, mg/dL	231.9 ± 53	231 ± 53	233 ± 54	.87
Mean daily BG, mg/dL	151.5 ± 35	156.6 ± 36	146.0 ± 34	.07
Mean fasting BG, mg/dL	133.9 ± 32	136.4 ± 35	131.2 ± 27	.55
% BG readings 70-180 mg/dL	76.2 ± 24	72.2 ± 24	80.5 ± 22	.01
% BG readings 181-240 mg/dL	15.5 ± 15	17.2 ± 15	13.8 ± 14	.07
% BG readings >240 mg/dL	7.7 ± 13	9.6 ± 14	5.7 ± 11	.06
HbA1c at randomization, %	7.88 ± 2.2	7.82 ± 2.2	7.92 ± 2.2	.74
HbA1c at 3 months, %	6.85 ± 1.1	6.82 ± 1.1	6.88 ± 1.1	.84
HbA1c at 6 months, %	6.70 ± 0.7	6.58 ± 0.7	6.82 ± 0.6	.69
Metformin therapy				
Continued metformin, n (%)	83 (59)	41 (56)	42 (63)	.43
Insulin therapy				
Total insulin, U/d	11.6 ± 9.8	12.0 ± 9.9	4.03 ± 1.7	.010
Total daily dose, U/kg/d	0.15 ± 0.1	0.15 ± 0.1	0.04 ± 0.02	.004
Total glargine, U/d	10.6 ± 7.4	10.6 ± 7.4	—	—
Total supplemental insulin, U/d	5.9 ± 4.0	6.9 ± 4.7	4.03 ± 1.7	.22
Hypoglycemia				
Number of BG tests, n	18,893	10,288	8,605	
Average BG testing/d, n	2.83 ± 0.87	2.93 ± 0.84	2.72 ± 0.89	.13
Patients with BG <70 mg/dL, n (%)	29 (21)	27 (37)	2 (3)	<.001
Patients with BG <54 mg/dL, n (%)	5 (4)	5 (7)	0 (0)	.06
Patients with BG <40 mg/dL, n (%)	2 (1)	2 (3)	0 (0)	.50
Episodes of BG <70 mg/dL, n (%)	139	136 (98)	3 (2)	
Episodes of BG <54 mg/dL, n (%)	11	11 (100)	0 (0)	
Episodes of BG <40 mg/dL, n (%)	3	3 (100)	0 (0)	
Glycemic variability				
Mean delta () daily BG, mg/dL	57.6 ± 37.8	65.7 ± 41.5	48.7 ± 31.2	.008
Standard deviation, mg/dL	39.5 ± 18.3	44.6 ± 19.7	33.9 ± 14.8	<.001
Complications, n (%)				
Composite of complications	38 (27)	22 (30)	16 (24)	.41
Acute kidney injury	3 (2)	2 (3)	1 (1)	.00
Urinary tract infection	9 (6)	6 (8)	3 (4)	.50
Mortality	2 (1)	0 (0)	2 (3)	.23

HbA1c, glycosylated hemoglobin; U, units; BG, blood glucose.

Data are mean ± standard deviation, unless otherwise noted. To convert HbA1c value in % to mmol/mol = $10.93 \times \text{HbA1c value} - 23.5$.

Composite of complications included urinary tract infections, pneumonia, diabetic foot infection, cardiac complications including myocardial infarction and heart failure, cerebrovascular accidents, and acute kidney injury and mortality.