A Randomized Controlled Study Comparing a DPP4 Inhibitor (Linagliptin) and Basal
Insulin (Glargine) in Long-Term Care Residents With Type 2 Diabetes

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I.   RESEARCH OBJECTIVES AND SPECIFIC AIMS

Diabetes mellitus is highly prevalent in the elderly, afflicting >25% of older adults aged 65-75 years and 40% of adults >80 years of age [1,2]. The prevalence of DM continues to increase in the United States, and older adults have the highest prevalence of any age group [3]. Between 2001 and 2010, the percentage of people with diabetes increased by 127% (9.1% to 20.7%) for those aged 65–74 years, and 126% (8.9% to 20.1%) for those aged 75 years and older [3]. The prevalence of diabetes in long-term care facilities (LTC) has been reported between 15% and 32% [4-7]. Elderly patients with diabetes have increased risk of complications compared to nondiabetic subjects [8-11]. Several observational studies have reported benefits of improved glucose control on the rate of metabolic complications and quality of life in elderly patients with diabetes [8-10]; however, no randomized clinical trials have determined best treatment strategies (insulin vs. oral agents) or what are the benefits of glucose control in clinical outcome and resource utilization in LTC residents.

In a recent observational study in LTC facilities [12] we reported i) a diabetes prevalence of 32.5% with most patients treated with oral antidiabetic drugs (OADs) alone or in combination with sliding scale regular insulin, ii) high frequency (44%) of hypoglycemic events, and iii) residents with hypoglycemia have a longer length of stay, emergency room or hospital transfers, and higher mortality compared to those without hypoglycemia (see preliminary results). In a pilot study in LTC patients with diabetes, we randomized 100 patients with diabetes to receive low-dose basal (glargine) insulin and rapid-acting insulin before meals or to continue OADs (metformin and/or sulfonylurea) plus regular insulin before meals for BG > 200 mg/dl. We observed similar improvement in HbA1c at 3 and 6 months and in the frequency of hypoglycemia (basal 28% vs. control 31%; please see preliminary results). The results of our preliminary studies indicate the need for safe and effective protocols to achieve glucose control with a low rate of hypoglycemia. We propose two strategies that have been shown to improve glucose control with low rates of hypoglycemia in the hospital, which could be easily implemented in LTC facilities [13,14]. The 'basal plus' approach with a daily dose of glargine plus correction doses of rapid-acting insulin was shown to be as effective as basal bolus regimen in improving glucose control in general medicine and surgery patients with type 2 diabetes (T2D) [13]. The sitagliptin inpatient trial [14] reported that treatment with DPP4 inhibitor alone or in combination with insulin glargine results in similar glucose control compared to a basal bolus regimen in inpatients with T2D. No clinical trials have determined the safety and efficacy of basal insulin (standard of care) and DPP4 inhibitors in LTC facilities. *Accordingly, we propose a prospective randomized controlled trial comparing treatment with a DPP4 inhibitor (linagliptin) to a basal plus (glargine) regimen (± metformin for both treatments) in LTC residents with T2D.*

Specific Aim and Hypothesis:

Aim 1. To determine whether glycemic control, as measured by change in mean BG, HbA1c and frequency of hypoglycemia, is different between treatment with linagliptin (Tradjenta®) and basal insulin in LTC residents with T2D. Patients with poorly controlled diabetes (HbA1c >7.5%) will be randomized to a 6-month intervention with linagliptin or glargine

insulin (± metformin for both treatments).

Hypothesis: Treatment with linagliptin, a once daily DPP4-inhibitor, will result in similar improvement in glucose control but in a lower rate of hypoglycemia than insulin treatment in LTC residents with T2D.

Aim 2. To determine differences in clinical outcome, resource utilization, and hospitalization costs between LTC residents with T2D treated with linagliptin and basal plus insulin. We will compare differences in complications (infectious and non-infectious, neurological and cardiovascular events), emergency room visits and hospitalizations between groups during the 6 months of intervention.

Hypothesis: Treatment with linagliptin will result in similar number of complications and resource utilization compared to insulin treatment in LTC residents with T2D diabetes.

II.   BACKGROUND AND CURRENT STATUS OF WORK IN THE FIELD.

Prevalence of diabetes in the elderly and long-term care facilities. The prevalence of diabetes mellitus increases with age, and it is estimated that more than 20% of older adults aged 65-75 years and 40% of adults >80years of age have diabetes [1,2]. The prevalence of diabetes in the elderly is expected to increase due to longer life expectancy and improve care of the population [2,15]. The estimated prevalence of diabetes in LTC facilities is reported to be ~ 15% to 32% [4], and in parallel to the increasing geriatric population, the number of LTC facilities is expected to rise [15].

Management of diabetes in the elderly and long-term care facilities. The goals of diabetes care in older adults, as in younger persons, include control of hyperglycemia and its symptoms, prevention and treatment of macrovascular and microvascular complications, and maintenance or improvement of general health status. Studies in adult patients with diabetes have clearly shown that improvement in glucose control results in reduction in long-term microvascular complications and in significant cost savings [9,10,16]; however, there are no prospective studies to determine the impact of improving glucose control on clinical outcome and health care cost in the elderly and LTC population. The management of diabetes in LTC residents is similar to that recommended for ambulatory patients with diabetes [17,18]; however, several factors complicate the management of hyperglycemia in this population [19]. Elderly people tend to have higher rates of comorbidities associated with aging such as premature death, functional disability, hypertension, coronary artery disease, cerebrovascular events, depression, cognitive impairment, urinary incontinence, falls, and pain. In addition, elderly patients with diabetes often experience changes in their nutritional intake and organ dysfunction, which increase the risk of complications and hypoglycemia [16,19-21]. Thus, benefits of improving glucose control must be balanced against the significant risks of side effects and hypoglycemia.

Current guidelines and position statements on diabetes management in LTC setting [11,22-24] are mainly based on consensus opinions or from extrapolations from studies involving middle-aged patients with diabetes. The 2013 American Diabetes Association guidelines recommend that older adults who are functional, cognitively intact, and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults [23]. In these subjects, a HbA1c level <7.0 %, a fasting glucose between 90-130 mg/dl, and a random glucose <180 mg/dl is recommended. Less intensive goals are recommended for patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment. Similarly, the American Geriatric Society recommends a goal HbA1c ≤7.5% in healthy adults with intact cognitive and functional status; however, a higher HbA1c, ranging from 8% to 8.5% is more appropriate in the presence of comorbidities, frailty, impaired cognitive and functional status and increased risk of hypoglycemia [11,24]. The European Diabetes Working Party for Older People

guidelines recommend a target HbA1c of 7-7.5% for patients without major co-morbidities while a higher target of 7.6-8.5% is proposed for frail patients with high risk of hypoglycemia [22,25]. More recently, the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes recommended an HbA1c target of 7%–7.5% but emphasized the need to individualize glucose goals based on comorbidities, cognitive and functional status [22]. All of these guidelines highlight the importance of avoiding hypoglycemia, as it has been associated with increased risk of complications and mortality in patients with diabetes [12,26-29].

Pharmacological therapy in elderly LTC residents with type 2 diabetes. Metformin is recommended as first choice OAD agent for the management of adult and elderly patients with type 2 diabetes [23,30]. However, it may cause anorexia, nausea, diarrhea, weight loss, and risk of lactic acidosis in patients with impaired renal and hepatic function [31,32]. Insulin secretagogues are effective in reducing glucose levels, but are associated with increased risk of hypoglycemia [33]. Thiazolidinediones improve insulin sensitivity but frequently cause weight gain, edema, osteopenia and are contraindicated in subjects with heart failure [33,34]. The α-glucosidase inhibitors delay carbohydrates absorption, but are associated with a high rate of GI side effects [32]. Few studies have addressed the safety and efficacy of DPP4 inhibitors in elderly patients [35,36]. DPP4-inhibitors; however, are promising agents in the elderly because they stimulate insulin secretion in a glucose-dependent fashion, thus not causing hypoglycemia when used as monotherapy or in combination with metformin therapy [37-39]. In addition, they have a low rate of side effects and can lower cardiovascular risks by reducing inflammation and oxidative stress, and by improving endothelial function [39-41]. Among FDA approved DPP4 inhibitors, linagliptin has unique PK and PD profile in the treatment of elderly LTC residents including a rapid-onset of action and efficacy in reducing fasting and postprandial glucose levels with low risk of hypoglycemia [42-44]. Linagliptin is rapidly absorbed after oral administration, with a maximum plasma concentration occurring after ~ 90 minutes, a long terminal half-life (>100 hours), and a short accumulation half-life of ~ 10 hours. It is eliminated primarily in feces, with only around 5% of the oral therapeutic dose excreted in the urine [45,46]. There are no clinically relevant alterations in linagliptin pharmacokinetics resulting from renal impairment or hepatic impairment [46-48].

Insulin therapy is widely recommended for diabetes management in LTC residents [49,50]. Clinical guidelines recommend initiating insulin when lifestyle modifications and oral agents fail or are contraindicated, and when random blood glucose levels are > 180 mg/dL [49,50]. These practice guidelines favor the use of physiologic (basal and nutritional-correction dose) insulin regimens over sliding scale regular insulin [51-53]. Basal insulin (glargine, detemir, NPH) is used alone or in combination with rapid-acting prandial analogs (lispro, aspart, glulisine) or regular insulin. The use of basal bolus insulin has been shown to improve glycemic control [54-56] and to reduce complications in general medicine and surgery patients in the hospital [56]; however, the use of a basal bolus approach is difficult to implement during periods of poor oral intake or in elderly LTC patients at risk of hypoglycemia. In our preliminary studies in LTC facilities, treatment with basal bolus improved glucose control but was associated with ~30% risk of hypoglycemia (see preliminary results). New insulin regimens such as basal plus approach [13] with a single dose of basal insulin and correction doses of rapid acting insulin if needed may represent an alternative to basal bolus resulting in similar glucose control and low rate of hypoglycemia in LTC residents.

Significance and Innovation. No prospective randomized trials have determined the best treatment strategies and the benefits of improved glucose control on clinical outcomes in residents in LTC facilities. In addition, no previous studies have reported on the relationship or association between glucose control, complications and hospitalization cost in LTC facilities. Our preliminary studies indicate that most LTC residents are treated with OADs alone or in combination with regular sliding scale or basal bolus insulin. More than 30% of LTC patients

with diabetes experienced hypoglycemia during a 6-month period, and those with hypoglycemia had more emergency room visits and hospital transfers, and higher mortality compared to residents without hypoglycemia. Thus, clinical trials aiming for improved glucose control and low rate of hypoglycemia are needed in this vulnerable population. This proposal aims to test the safety and efficacy of two novel treatment approaches in LTC facilities – the basal plus insulin regimen and DPP4 inhibitors. Both of these regimens were recently reported to be effective in improving glucose control with low rate of hypoglycemia in the hospital setting [13,14] and could be easily implemented in LTC setting. We selected the use of linagliptin in this proposal due to its safety and no dose adjustment needed in elderly patients with reduced kidney function. Although basal insulin and DPP4 inhibitors represent promising treatment alternatives to basal bolus insulin regimen or other treatment modalities, randomized clinical studies are needed to determine their efficacy and safety in the management of elderly patients in LTC facilities.

This proposal is innovative and will provide important novel clinical information. This is the first prospective RCT to compare glucose control, resource utilization and hospitalization costs between treatment with insulin and DPP4 inhibitors, alone or in combination with metformin, in LTC residents with type 2 diabetes. It is not known if insulin therapy, which may be expected to result in lower daily glucose and HbA1c but in higher number of hypoglycemic events, will reduce infectious and noninfectious complications and lower resource utilization and costs compared to patients treated with DPP4 inhibitors. In this trial, we selected two treatment regimens that have been proven to be effective in improving glucose control with a low rate of hypoglycemia and could become standard of care for elderly LTC residents with type 2 diabetes.

III. PRELIMINARY RESULTS:

Basal Bolus insulin trials in hospitalized patients with diabetes. We have reported several prospective, randomized multi-center trials that show that treatment with basal or basal plus prandial insulin regimens are superior to sliding scale alone for the treatment of general medicine and surgery patients with T2D [10,54]. In addition, the Rabbit Surgery trial [57], reported similar improvement in glucose control and lower rate of a composite of complications including wound infection, pneumonia, respiratory failure, renal failure, and bacteremia in general surgery patients. In these studies, the rate of hypoglycemia with the use of basal bolus approach in the hospital setting ranged between 3% and 32% [54-56].

Basal Plus approach in general patients with T2D. The recently reported Basal Plus trial [58] recruited 375 patients with T2D treated with diet, oral antidiabetic agents or low-dose insulin (≤ 0.4 unit/kg/day) to receive a 'Basal Bolus' regimen with glargine once daily and glulisine before meals, a 'Basal Plus' regimen with glargine once daily and supplemental doses of glulisine, and sliding scale regular insulin (SSI). This trial reported that treatment with basal plus corrections resulted in similar improvement in glycemic control and in the frequency of hypoglycemia compared to a standard basal bolus regimen. In addition, treatment with basal bolus and basal plus resulted in less treatment failures than treatment with SSI. A BG <70 mg/dL occurred in 16% of patients in basal bolus and 12% in basal. We concluded that the use of a basal plus regimen is an effective alternative to basal bolus in general patients with T2D.

Fig 2- Sitagliptin Inpatient trial

Sitagliptin Inpatient Pilot Study [14]. In a two-center open-label randomized pilot trial we recently determined differences in glycemic control between sitagliptin alone or in combination with basal insulin and basal bolus regimen in medicine and surgery patients with T2D (Figure 3). In this study, 90 patients with a BG between 140-400 mg/dl treated with diet, OAD or low-dose insulin (≤ 0.4 U/kg/day) were randomized to sitagliptin once daily (n=30), sitagliptin and basal insulin (n=30) and to a basal bolus (n=30) regimen. Treatment with sitagliptin alone or in combination to glargine resulted in similar glycemic control compared to basal bolus. There were no differences in hypoglycemia, frequency of treatment failures, length of stay or hospital complications. These results indicate that treatment with a DPP-4 inhibitor is safe and effective in the hospital management of T2D [14].

Cost Analysis of Diabetes Care in General Surgery Patients. Adeel et al. 73rd ADA meeting, June 2013. A post-hoc cost analysis of hospitalization costs and charges in the RABBIT Surgery trial revealed that improvement of glucose control using basal bolus resulted in significantly lower hospital costs than treatment with sliding scale insulin (SSI) ($23.8±11 vs. $29.4±19 K USD, p=0.03). Subgroup analysis on each complication revealed that the total hospital cost for patients with wound infection was approximately 2 times higher than those without them ($45.5±33 vs. $26±15 K USD, p=0.02), and that the hospital cost for those with pneumonia or bacteremia was 3 times higher than those without complications ($71.5±41 vs. $26±14 K USD, p=0.001, and $67.5±47 vs. $26±14 K USD,

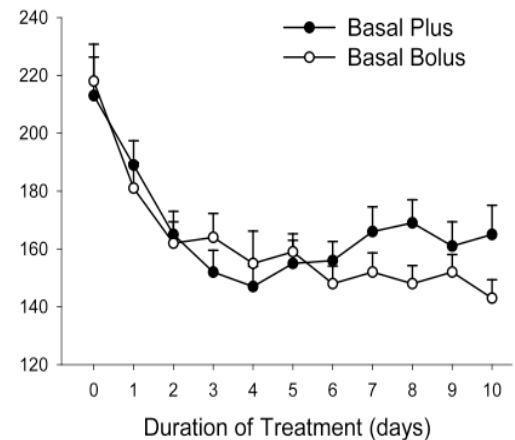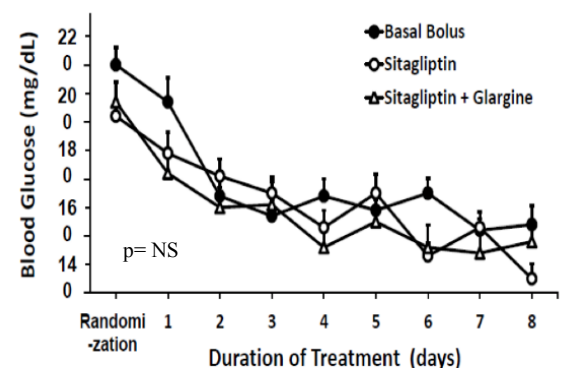p=0.006 respectively). These results indicate that improvement of BG control reduces hospital complications, perioperative complications and resource utilization, and hospitalization cost in patients undergoing general surgery.

Diabetes and Clinical Outcome in Long-term Care Residents [12]. This observational study analyzed the quality of diabetes care, glycemic control, and clinical outcome in 1,409 subjects admitted to 3 community LTC facilities in Atlanta. The prevalence of diabetes was 34.2%. On admission, patients with diabetes were either on no pharmacological agents (10%) or were treated with, sliding scale regular insulin (SSI, 25%), OADs (5%), insulin (34%), or with combination of OADs and insulin (26%). Patients with diabetes had higher number of complications (p<0.001) and required more emergency room and hospital transfers (p=0.013). A Cox proportional hazards model revealed that a history of diabetes is associated with a higher risk of mortality (HR: 1.44, p=0.027). A total of 42% of patients had ≥ 1 episode of BG <70 mg/dl and 7% had a BG <40 mg/dl. Hypoglycemia was reported in 45% on OADs (mostly sulfonylurea plus SSI), 53% on glargine, 67% on NPH or premixed insulin, 20% patients on SSI alone. Patients with hypoglycemia had a longer length of stay (p<0.001), higher emergency room or hospital transfers (44% vs. 30%; p= 0.004) and higher mortality (18% vs. 10%, p=0.015). These results indicate that diabetes is common in LTC and is associated with higher resource utilization and complications, and that hypoglycemia is associated with increased rates of emergency room care and hospitalization, length of stay, and mortality [12].

Randomized Controlled Pilot Study on the Efficacy and Safety of Basal Bolus Insulin Regimen in Long-Term Care Residents. This pilot, prospective, RCT randomized patients from 2 LTC university-affiliated facilities with A1C >7.5%, treated with diet and/or with stable dose of OADs to glargine (starting at 0.1 U/kg/day) plus correction doses of glulisine before meals for BG > 200 mg/dl, n=46) or to continue OAD and sliding scale insulin before meals (n=54) for 26 weeks. Primary endpoints were differences in mean fasting and daily BG, change in A1C, and hypoglycemia (<70 mg/dl). There were no differences in daily glucose or with the A1C at 3 months (149±28 vs 136±26 mg/dl and 7.5±0.7% vs 7.2±0.8%, p= NS) or at 6 months (172±19 vs 148±27 mg/dl and 6.7±0.1% vs 6.6±0.9%, p NS) or in the number of patients with hypoglycemia (basal 28% vs. control 31%, p=0.37). The results of this study suggest that patients in LTC facilities can achieve similar improvement in glycemic control, without differences in mean daily BG, hypoglycemia with basal insulin or with OADs and SSI supplements.

Table. Glycemic control at 3 and 6 month therapy with basal bolus and OADs plus sliding scale

	Basal Insulin	OAD + SSI
Fasting BG at 3 mo, mg/dl	132±27	123±24
Daily BG at 3 mo, mg/dl	159±30	138±27†
Fasting BG within 80-180 mg/dl, %	95	96
A1C at 3 months, %	7.5±0.7	7.2±0.8
Fasting BG at 6 mo, mg/dl	132.4±27	123.0±24
Daily BG at 6 mo, mg/dl	159.6±30	137.6±27
A1C at 6 months, %	6.7±0.1	6.6±0.9
*p=<0.05; †p<0.01		

Summary: These preliminary studies highlight our experience in conducting RCT and cost analysis studies in patients with diabetes in the hospital and LTC facilities. Our preliminary studies indicate that diabetes is common in LCT residents and is associated with higher resource utilization, and that treatment-related hypoglycemia is associated with increased rates of emergency room care and hospitalization, and mortality. In our cross-sectional study, we observed that 44% patients with diabetes had ≥ 1 episode of BG <70 mg/dl. Patients with

hypoglycemia had a longer length of stay, higher emergency room or hospital transfers, and higher mortality compared to those without hypoglycemia. In our pilot RCT, basal bolus insulin and OAD plus sliding scale regular insulin resulted in similar in glucose control, complications and in ~30% rate of hypoglycemia indicating the need for effective treatment regimens with lower rates of hypoglycemia. The proposed RCT will provide clinically important and novel information on glucose control, clinical outcome, resource utilization and hospitalization costs in LTC residents with type 2 diabetes treated with basal insulin and DPP4 inhibitor.

IV. EXPERIMENTAL PLAN

Aim 1. To determine whether glycemic control, as measured by change in mean BG, HbA1c and frequency of hypoglycemia, is different between treatment with linagliptin (Tradjenta®) and basal insulin in LTC residents with T2D.

IV.a. Rationale. Diabetes affects one-third of elderly patients in LTC facilities [4-7]. Management of hyperglycemia in LTC residents is challenging because of the high prevalence of comorbidities, organ dysfunction, and changes in nutritional intake that could increase the risk of hypoglycemia [19]. Most patients in LTC facilities are managed with OADs alone or in combination with insulin with a reported ~30% incidence of hypoglycemia [49,50]. LTC residents with hypoglycemia require more emergency room and hospital transfers, as well as higher mortality compared to those without hypoglycemia [12]. Our recent 'basal plus' approach with a daily dose of glargine plus correction doses with rapid-acting insulin is as effective as basal bolus regimen in patients with T2D, with low rates of hypoglycemia [13]. Similarly, the recent Sitagliptin Inpatient Trial [14], reported that treatment with sitagliptin alone or in combination with low-dose glargine result in similar glucose control compared to basal bolus regimen in medicine and surgery patients. The efficacy of basal plus regimen and DPP4 inhibitors in lowering blood glucose with a low-risk of hypoglycemia make these treatment ideal for the management of elderly; however, no clinical studies have determined their efficacy and safety in LTC facilities. *Accordingly, we propose a prospective randomized controlled study to test the efficacy and safety of a DPP4 inhibitor and basal insulin for the management of LTC residents with type 2 diabetes.*

IV.b. STUDY DESIGN AND METHODS

A total of 150 male or female LTC residents with type 2 diabetes with an fasting or random BG >/= 180 mg/dL and/or an A1c > 7.5% while receiving treatment with diet (no pharmacological therapy), OADs (metformin, secretagogues, thiazolidinediones), low dose insulin of 0.1U/kg/day or sliding scale regular insulin will be randomized to receive linagliptin or glargine insulin therapy.

This study will be performed at Crestview, a community LTC institution affiliated with Grady Health System; Budd Terrace on the Wesley Woods campus of Emory University; and the Community Living Center at the Atlanta VA Medical Center, Atlanta.

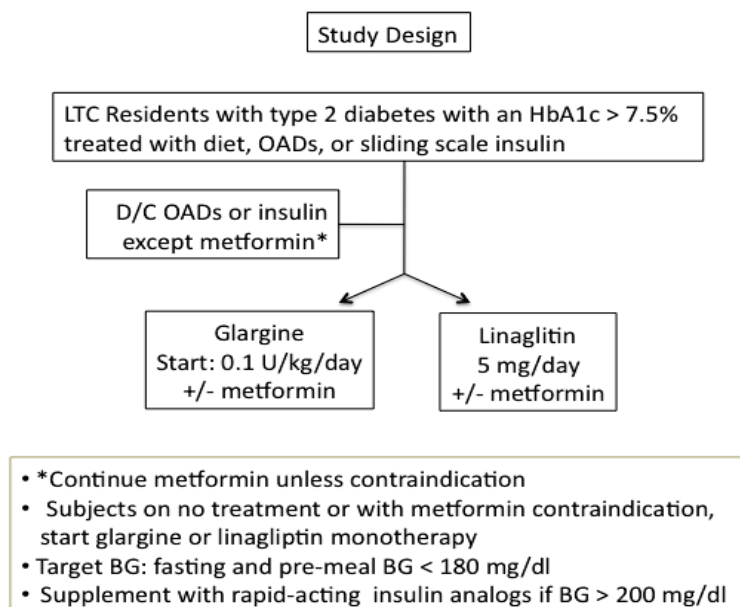## IV.c. Primary and Secondary Research Outcomes:

The <u>primary endpoint</u> of the study is change in mean BG over a 6-month treatment period between treatment with basal plus insulin regimen and aDDP4 inhibitor in LTC residents with poorly controlled diabetes.

<u>Secondary outcomes</u> include differences between treatment groups in any of the following measures:
1. Percentage of HbA1c ≤ 7.5% at 3 or 6 month independent of the occurrence of hypoglycemia.
2. Occurrence rate and total number of hypoglycemic events (<70 mg/dl) and severe hypoglycemia (< 40 mg/dl).
3. Total daily dose of insulin, metformin and linagliptin.
4. Change in hemoglobin A1c over a 6-month treatment period
5. Changes in cognitive function assessed by mini-mental examination.
6. Prevalence of acute complications (urinary tract infections, pneumonia), bedsores, diabetic foot infection.
7. Need for emergency room visits or hospitalizations during the study period.
8. Cardiac complications are defined as myocardial infarction, cardiac arrhythmia and heart failure.
9. Acute renal failure defined as a clinical diagnosis of acute renal failure with documented new-onset abnormal renal function (increment > 0.5 mg/dL from baseline).

10. Hospital mortality. Mortality is defined as death occurring during admission.

IV.d.   Plan. This study will include male or female subjects admitted to LTC affiliated with Grady Health System, Emory University Hospital, and VAMC in Atlanta, Georgia. Due to the design of this study (i.e. enrollment of subjects admitted for LTC), there will be no run-in period. All residents with a known history of diabetes and an HbgA1c >7.5% despite treatment with diet (no pharmacological therapy), stable dose of OADs (metformin, secretagogues, thiazolidinediones), or sliding scale insulin therapy will be considered as potential candidates in this study. The consent form will be presented and discussed to primary care team, and participants and/or relatives prior to participation in the study.

Study Design

LTC Residents with type 2 diabetes with an HbA1c > 7.5% treated with diet, OADs, or sliding scale insulin

D/C OADs or insulin except metformin*

Glargine
Start: 0.1 U/kg/day
+/- metformin

Linaglitin
5 mg/day
+/- metformin

- *Continue metformin unless contraindication
- Subjects on no treatment or with metformin contraindication, start glargine or linagliptin monotherapy
- Target BG: fasting and pre-meal BG < 180 mg/dl
- Supplement with rapid-acting insulin analogs if BG > 200 mg/dl

- Patients receiving no pharmacological agents will be randomized to receive once daily linagliptin or glargine insulin as monotherapy.

- Patients receiving OADs will discontinue these agents at enrollment with the exception of metformin (unless contraindication). Patients will continue therapy with metformin at the same dosage and will start combination therapy with linagliptin or glargine insulin (add-on therapy).

- Patients who are not candidate to metformin therapy (i.e., reduced kidney function or GI intolerance) will be treated with once daily linagliptin or glargine insulin as monotherapy.

- For safety reason, patients in both groups will receive supplemental (correction) doses of rapid-acting insulin (lispro or aspart) before meals for BG > 200 mg/dl.

- The goal of therapy is to maintain fasting and pre-meal blood glucose <180 mg/dL and an A1C <7.5% while avoiding hypoglycemia.

IV.e.   Study Groups:

Group 1. Basal Plus regimen with glargine once daily ± metformin, n= 75

Group 2. Linagliptin once daily ± metformin,, n=75

GROUP 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
- Start accuchecks with meals and at night. Can reduce to twice a day when appropriate.

GROUP 2. Glargine Insulin Group

- Discontinue oral antidiabetic drugs (except metformin if no contraindication), insulin and non-insulin injected antidiabetic medication on admission.
- Start accuchecks with meals and at night. Can be reduce to twice a day when appropriate.
- 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 follow:
  - Fasting and pre-meal BG between <180 mg/dl without hypoglycemia the previous day: no change
  - Mean fasting and pre-meal BG between 181-280 mg/dl without hypoglycemia: increase glargine dose by 10% every 3 days
  - Mean fasting and pre-meal BG >281 mg/dl without hypoglycemia: increase glargine dose by 20% every 3 days
  - Mean fasting and pre-meal BG between <100 mg/dl: decrease glargine dose by 10% every day
  - 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 30-40%.

- **Blood glucose monitoring.** Blood glucose will be measured before each meal (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician.

IV.f. Investigational drugs.
1. Linagliptin (Tradjenta®) 5 mg tablets for oral administration. Linagliptin is not a formulary drug at Grady Health System and VAMC and will be provided by Boehringer Ingelheim Pharmaceuticals, Inc (see letter of support, page 76)
2. Glargine insulin: U-100/mL, provided in 10 mL vials. Glargine (Lantus®) is available in all institutions.

IV.g. Withdrawal Criteria
1. The subject may withdraw at any time during the study by primary care provider or research team.
2. The subject may be withdrawn at the investigator's discretion due to a safety concern or if judged non-compliant with trial procedures or for contravention to the inclusion and/or exclusion criteria.
3. Subject diagnosed with acute pancreatitis by clinical and/or radiographic criteria.
4. Patients with severe hyperglycemia defined as 3 consecutive BG levels > 280 mg/dl or 2 consecutive days with an average BG > 280 mg/dL will be considered as failure and discontinued from the study. Patients receiving linagliptin therapy will be switched to basal plus insulin and those on basal insulin will be switched to basal bolus insulin regimen.

IV.h.   Subject Replacement
There will be no replacement of subjects in this trial.

IV.i.   During follow up we will collect the following information
1. Glycemic control:
    a. Mean daily fasting and premeal blood glucose levels.
    b. HbA1c at baseline, 3 and 6 months of discharge
    c. Number of hypoglycemic events
2. Diabetes treatment:
    a. Number of patients receiving supplements and dosage as well as metformin therapy.
    b. Protocol adherence by LTC facility
3. Clinical Outcome (see Aim 2):
    a. Hospital readmissions, emergency room visits, infectious and non-infectious complications

V. Aim 2. To determine differences in clinical outcome and resource utilization between treatment with linagliptin and basal insulin in LTC residents with T2D.

Rationale. Benefits of improved glucose control on clinical outcomes and hospitalization costs in elderly residents in LTC facilities have not been determined in prospective RCT. This study will compare differences in complications (infections and non-infection, neurological and cardiovascular), resource utilization and hospitalization costs between basal insulin or with linagliptin therapy. We expect that patients treated with basal insulin may have lower daily glucose and HbA1c levels, but higher number of hypoglycemic events. It is not clear if the lower glucose and HbA1c levels will reduce complications, resource utilization and costs compared to patients treated with DPP4 inhibitors who may experience less glucose control but lower hypoglycemic events.

V.a. Data collection and data entry. Baseline and daily information will be entered by the study coordinators into data collection paper forms and into an electronic database (RedCap) provided by the Emory Research Information Technology Department.   Baseline data will include demographics/history form (subject gender, age, ethnicity, type of treatment and comorbid conditions, body weight, BMI, laboratory results. Daily information will be collected on treatment, nutrition, blood glucose and laboratory values, hospital complications and adverse events (hypoglycemia).

V.b. Resource utilization. We will prospectively collect information on emergency room visits and hospitalizations, laboratory, pharmacy, consultation services and radiology services, as well as presence of complications including pneumonia, acute myocardial infarction, heart failure, acute renal failure, wound infections and bedsores, cerebrovascular events, and other complications.

V.c. Financial assessment. The Analytic Information Warehouse (AIW) infrastructure program will be utilized to support extraction, mapping and modeling of electronic health record information from Grady and Emory health records and billing systems. The AIW infrastructure is designed to allow analysts to transform heterogeneous sets of variables into systematically defined core set of data elements. Data will be collected prospectively and also extracted for each patient using ICD-9 codes for demographics, complications, and use of resources including laboratory, radiology, and pharmacy utilizations as well as total charges during the study period. Differences will be expressed by applying Medicare Cost Report cost-to-charge ratios to the charge data using Medicare Hospital Cost Report publish by the Centers of Medicare and Medicaid Services (CMS) (https://wwws.gov/CostReports/02_HospitalCostReport.asp). Based on CMS review of Emory

Long Term Care facilities 2012 cost report, the inpatient cost to charge ratio will be 0.421 for patients admitted in 2013. Data set will be queried to allow analysis of complications, laboratory, pharmacy, consultation services and radiology costs.

V.d. Assessment and Monitoring of Nosocomial Infections. Nosocomial infections will be diagnosed based on standardized CDC criteria [59]. New infections will not be diagnosed until 48 hr after study initiation to minimize the chance that the infection was actually present prior to study initiation.

V.e. Monitoring of renal function. Acute renal failure is defined as an increment > 0.5 mg/dl from baseline.

V.f. Cerebrovascular accident. Defined as neurologic deficit persisting > 72 hr, transient ischemic attack, deficit resolving within 24 hours, or deficit lasting > 24 - < 72 h (reversible ischemic neurologic deficit).

V.g. Major Cardiovascular Events (MACE). All outcome data will be defined per standard American College of Cardiology–American Heart Association definitions:
- Acute myocardial infarction: (1) increase in troponin and creatine kinase (MB) markers with at least one of the following: (a) ischemic symptoms, (b) development of pathologic Q waves on EKG, (c) electrocardiographic changes indicative of ischemia (ST-segment elevation or depression), or (d) coronary artery intervention (e.g., coronary angioplasty) [60].
- Congestive heart failure on chest radiograph and with appropriate clinical symptoms/signs [60].
- Cardiac arrhythmias: malignant arrhythmia [asystole, ventricular tachycardia or fibrillation] [60] .

VI. Methods and Procedures Applied to Human Subjects:

VI.a. Subject Population:
This study will include 150 LTC facility residents with a known history of type 2 diabetes. Patient selection will be determined by the set of inclusion and exclusion criteria.

VI.b. Inclusion Criteria:
1. Males or females with known history of type 2 diabetes, treated with diet, OADs as monotherapy or in combination therapy (excluding DPP4 inhibitors), low dose insulin of 0.1U/kg/day or sliding scale insulin.
2. Subjects with HbA1c > 7.5% or BG >/= 180 mg/dL.

VI.c. Exclusion Criteria:
1. Subjects with a history of type 1 diabetes or with a history of diabetic ketoacidosis [61].
2. Treatment GLP1 analogs during the past 3 months prior to admission.
3. Recurrent severe hypoglycemia or hypoglycemic unawareness.
4. Subjects with history of gastrointestinal obstruction or gastroparesis.
5. Patients with acute or chronic pancreatitis or pancreatic cancer.
6. Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease, portal hypertension) and elevated ALT and AST > 3 times upper limit of normal, or significantly impaired renal function (GFR < 45 ml/min).
7. Treatment with corticosteroids, parenteral nutrition and immunosuppressive treatment.
8. Mental condition rendering the subject unable to understand the nature and scope of the study.

VII. CLINICAL MANAGEMENT GUIDELINES

VII.a. Admission Laboratory Studies

Standard of care laboratory studies including glucose, HbA1c, chemistry, hematology, and urine will be measured on admission and as determined by the treating physician.

VII.b. Treatment of Hypoglycemia

Hypoglycemia (glucose <70 mg/dL) will be treated following approved protocol.

- If patient is alert and can tolerate oral intake, give 20 grams of fast-acting carbohydrate.
- If patient not alert and cannot tolerate oral intake, give1ampule (25 mL) IV of Dextrose 50%, or 1 amp of glucagon IM or SC
- Check finger stick BG q 15 minutes and repeat above treatment until BG > 100 mg/dL.
  - If BG < 70 mg/dL, call MD and repeat hypoglycemia orders (above)

VIII.   STATISTICAL ANALYSIS

VIII.a.   Sample Size and Power Calculations: This study is randomized, open-label controlled trial. The primary endpoint in this study is glycemic control measured change determined by mean daily blood glucose concentrations and in HbA1c at 3 and 6 months of intervention. The median stay at all facilities was 48.9±50 days, therefore the study did not have power to determine a statistical change in glycated hemoglobin at 6 months. The primary endpoint of the study was modified to evaluate the difference between treatment with basal insulin and linagliptin on glycemic control determined by mean daily blood glucose concentrations during LTC stay, as previously reported ([62]). Main secondary endpoints included differences in the frequency of hypoglycemia, fasting glucose, HbA1c at 3 and 6 months of intervention, complications, emergency room visits and hospitalizations. We made the comparisons using non-parametric Wilcoxon tests for continuous variables and χ2 tests (or Fisher's exact test) for discrete variables. We summarize demographics, baseline clinical characteristics, and clinical outcomes by the two treatment groups. Data is presented as mean ± standard deviation for continuous variables and present count (percentage) for categorical variables. Glycemic variability was calculated by standard deviation (SD) of glucose values during entire study and by the mean daily delta (Δ) daily range of blood glucose (daily max – daily mini- mum)(20, 24).The data were 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.

VIII.b. Analysis of Primary Endpoint:

To compare differences between treatment groups on glycemic control determined by mean daily blood glucose concentrations. We defined non-inferiority 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 non-clinically significant in the hospital setting, and is smaller than significant treatment effects in other superiority trials [58,63,64] Based on our preliminary data in LTC [62], we assumed a standard deviation of 40 mg/dl change is bounded above by 1%. With a one-sided two-sample t-test, alpha=0.05, with Bonferroni correction applied to adjust for multiple comparisons across different days on therapy, and after adjusting for 10–15% attrition, a total of 64 patients were required for both the linagliptin and the basal group to ensure 80% power to reject the non- inferiority hypothesis. This leads to a final total sample size estimate of 140 participants.

VIII.c. Analysis of Secondary Endpoints: Secondary endpoints include outcomes on hypoglycemia, complications, HbA1c, resource utilization and costs. For hypoglycemia outcomes, we will first conduct nonparametric comparisons of the rate of hypoglycemia based on a two-sided Chi-square test (or Fisher's exact test in the presence of low incidence rates), followed by the Cochran-Mantel-Haenszel test, which adjusts for the potential center effect. Univariate Poisson regression (or Negative Binomial regression) will be performed to assess whether there is any difference in the number of hypoglycemia events between the two treatment groups. We will further conduct multivariate Logistic regression, Poisson regression (or negative binomial

regression) to estimate the difference in the rate and frequency of hypoglycemia while adjusting for relevant covariates. Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures, such as deviance residual plot and Hosmer-Lemeshow test, will be applied to examine the fit of the developed models.

The primary cost outcome is the overall resource utilization converted to cost figures based on cost-to-charge ratio. We will first compare the overall cost between groups using two-sample t-tests or nonparametric Wilcoxon tests. We will perform multivariate linear regression to evaluate the group difference while accounting other possible confounders. To address the potential skewness of cost distribution, we may adopt Log or other appropriate transformations. We will also consider multivariate median regression, which is expected to be more robust in the presence of outliers compared to linear regression. Model selection and model checking will be performed in multivariate analyses.

For other secondary endpoints such as itemized resources utilization, complications, need for emergency room and hospitalization we will use the analytic strategy proposed for the primary endpoint to analyze continuous secondary outcomes, and the approach proposed for the hypoglycemia outcome to analyze other discrete secondary outcomes. A p-value less than 0.05 will be considered significant. Statistical analysis will be performed using the SAS (version 9.2; SAS Institute, Cary, NC).

IX.   Potential Risks to the Subject:

Hypoglycemia. Hypoglycemia is defined as capillary and/or laboratory glucose <70 mg/dL and severe hypoglycemia is defined as glucose < 40 mg/dL. We expect that ~20% of subjects treated with basal insulin will experience hypoglycemia and < 5% in patients treated with linagliptin.

Hyperglycemia. In the Basal Plus Trial and Sitagliptin trial, 12-18%% of patients had glucose readings >200 mg/dL. We expect that < 20% of BG readings in subjects treated with basal plus regimen or with linagliptin plus rapid-acting insulin analogs will have a glucose > 200 mg/dl. In this analysis, severe hyperglycemia is defined as a capillary and/or laboratory BG >300 mg/dL.

X.   Protection against Risks:

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary blood glucose using hand-held glucose meters, b) only experienced nurses/or phlebotomist will draw blood samples, and c) no patients with significant liver and renal impairment will be recruited in this study.

Hypoglycemia: We expect that approximately 12% of subjects treated with basal plus and < 5% of linagliptin group will experience one or more episodes of hypoglycemia. Hypoglycemia will be treated with standard treatment protocols available at each institution.

Hyperglycemia: supplemental insulin will be given before meals to cover for BG >200 mg/dl. Patients with persistent hyperglycemia defined as 3 consecutive BG levels > 280 mg/dl or 2 consecutive daily average >15.5 mmol/L (280 mg/dL) will be considered as failure and will be discontinued from the study. Patients receiving linagliptin will be switched to basal and those on basal will be switched to basal bolus regimen.

Acute renal failure: patients with GFR <45 ml/min will not be treated with metformin.

XI. Data handling and record keeping: Data collection records with personal identifiers will be stored in locked file cabinets. No blood samples will be stored in this study. Access to research will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

XII. Storage and Drug Accountability of Study Medication(s). Linagliptin will be stored and dispensed by the research pharmacy at each institution. Glargine insulin is standard of care and is available at the three participating institutions and will be dispensed by general inpatient pharmacy.

XIII. Randomization and Blinding. This is an open label randomized controlled trial. Patients will be randomized consecutively using a computer generated randomization table provided by Dr. Limin Peng at the Emory School of Public Health. The randomization table will be mailed to the research pharmacist at each institution who will be in charge of the randomization and group assignment.

XIV. Informed Consent. . Informed consent will be obtained before any trial related procedures including screening procedures. The consent form will follow the IRB guidelines of Emory University. A signed copy of the consent will be provided to the participant and a copy of the consent will be placed in the study office.

XV. Inclusion of women: We anticipate that ~50% of the study subjects will be female.

XVI. Inclusion of minorities: Patients will not be excluded based on race or ethnic origin. We anticipate that half of patients will be African Americans, 10% Hispanics, and the rest Caucasians.

XVII. Inclusion of children: No patients under the age of 18 will be recruited in this study.

XVIII. Financial Conflict of Interests. None of the investigators in this study have any outside activities that may represent a conflict of interest.

XIV. Data Safety Monitoring Plan.
A Data Safety Monitoring Board or Safety Officer has been designated for this study.

Mary Rhee, MD
Department of Medicine/Endocrinology

Catherine Barnes, Ph.D.
Department of Medicine/Endocrinology

The frequency of protocol review will be: every 6 months.

The PI will forward reports of safety reviews within 15 days of the meeting to the Emory IRB.

See full Data safety monitoring plan in the attachment labeled Data Safety Monitoring Plan.

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