Title: **Prevention of stress hyperglycemia with the use of DPP-4 inhibitors in non-diabetic patients undergoing non-cardiac surgery, a Pilot Study (SITA-SURGERY PILOT TRIAL).**

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ABSTRACT

Approximately 51.4 million surgical procedures are performed in the United States each year.[1] Over 40% of patients both with and without diabetes (DM) develop stress hyperglycemia (defined as a BG >140 mg/dl) after general surgery.[2,3] Compared to patients without DM, those with DM have higher rates of complications that include wound infections,[4,5] acute renal failure,[6] longer hospital stay,[7,8] and perioperative mortality.[8,9] However, non-DM patients with stress hyperglycemia have poor surgical outcome after cardiac surgery with even higher rates of complications and mortality compared to those with DM.[10,11] Few observational studies looking at non-cardiac patients have found that stress hyperglycemia is associated with higher rates of complications including mortality and length of stay compared to either normoglycemia[12] or known DM.[2,13] Although there is no consensus on optimal glycemic targets, there is strong agreement that improvement in glycemic control reduces complications and inpatient mortality,[14-16] with better apparent response in subjects with stress hyperglycemia compared to those with known DM.[17] In the GLUCO-CABG trial,[18] we reported no differences in a composite of complications between intensive and conservative insulin regimens in patients with DM; however, we observed a significant reduction in hospital complications in patients with stress hyperglycemia treated with intensive glucose control (see preliminary results). These data clearly indicate that stress hyperglycemia is an independent risk factor of morbidity and mortality in cardiac and general surgery.[4,7,19-21]

Our group recently reported that inpatient therapy with oral dipeptidyl peptidase-4 inhibitor (DPP4-I) is an effective alternative to insulin in improving glycemic control with low risk of hypoglycemia in general medicine and surgical patients.[22] In addition, our preliminary studies indicate that sitagliptin is effective in preventing the need for subcutaneous insulin therapy during the transition period from the ICU to regular floors in patients with stress hyperglycemia (see preliminary data). To our knowledge, no prospective studies have determined best treatment to prevent and/or treat stress hyperglycemia among non-DM patients undergoing non-cardiac surgery. Therefore, this proposal will address the following 3 important clinical questions: 1) can stress hyperglycemia be safely prevented with the use of a DPP4-inhibitor, a commonly used drug for the treatment of patients with type 2 diabetes with no increased risk of hypoglycemia?, 2) Can treatment with a DPP4-inhibitor reduce the need for

insulin therapy and reduce risk of hypoglycemia?, and 3) does prevention of stress hyperglycemia reduce perioperative complications during the perioperative period?.

SPECIFIC AIM
To determine whether treatment with sitagliptin once daily can prevent the development of stress hyperglycemia during the postoperative period in non-diabetic patients undergoing general surgery.
Hypothesis: We hypothesize that sitagliptin, an oral DPP4-inhibitor, will prevent the development of perioperative hyperglycemia and its complications in non-diabetic patients undergoing non-cardiac surgery.

BACKGROUND REVIEW
Stress hyperglycemia in the hospital. Stress hyperglycemia is reported in over 30-40% of medicine and surgery patients in the hospital,[2,23,24] and in up to 80% after cardiac procedures.[3,6,25] Large cohort studies have identified hyperglycemia and DM as independent risk factors of poor outcome after surgery compared to patients with normoglycemia, specifically higher perioperative mortality,[8,9] deep sternal wound infections,[4,5] renal failure,[6] postoperative strokes,[7,26] longer hospital stays,[7,8] and higher health care resource utilization.[27-29] In patients undergoing non-cardiac (general) surgery, diabetes as well as hyperglycemia in non-DM patients are associated with up to 4-fold increase in complications and over a 2-fold increase in death compared to patients with normoglycemia.[12,30,31] Solid evidence indicates that stress hyperglycemia in non-DM patients is associated with worse clinical outcome compared to patients with a known history of DM.[2,10,11,13,32-34] The severity of hyperglycemia positively correlates with the rates of complications among non-DM patients but not in those with DM.[30] The risk of post-operative infections increase incrementally with worsening hyperglycemia, independent of DM status.[35] Despite the relationship between stress hyperglycemia in non-DM patients and poor outcomes, few non-DM patients with stress hyperglycemia are treated with either oral agents or insulin.[13]

Glycemic control in surgery and critically ill patients. The results of several clinical trials in critically ill and surgery patients indicate that improvement of glycemic control reduces LOS, risk of multi-organ failure and systemic infections,[5,14,36] as well as mortality in patients with stress hyperglycemia and diabetes.[14,37] The Portland Diabetic Project, a prospective, non-randomized study of diabetic patients who underwent CABG[5] reported that the use of continuous insulin infusion (CII) to achieve a BG target between 150-200 mg/dl compared with SQ regular insulin resulted in a lower mortality rate (2.5% vs. 5.3%) and reduced rate of deep sternal wound infection by 66%.[38] In the GLUCO-CABG trial (see preliminary results) we found no differences in a composite of complications between intensive and conservative regimens in patients with DM; however, we observed a reduction in hospital complications in patients with stress hyperglycemia treated with intensive glucose control.[18] Similarly, a subgroup analysis by Van den Berghe et al[39] of surgical and medical ICU patients reported that while glucose lowering effectively reduced mortality in those without a previous history of diabetes, no significant benefit from treatment was observed in patients with diabetes. The Surgical Care and Outcomes Assessment Program performed a retrospective review if 11,633 patients with and without DM undergoing surgery and found that glycemic control with insulin treatment reduced the rates of complications.[31,40]

Stress hyperglycemia: mechanisms and consequences. The ADA/AACE and Endocrine Society guidelines on inpatient hyperglycemia defined stress hyperglycemia or hospital-related hyperglycemia as any BG concentration >140-180 mg/dl without evidence of previous diabetes. In most patients stress hyperglycemia resolves as the acute illness or surgical stress abates; however ~30% to 60% of patients have impaired carbohydrate intolerance[41] or unrecognized diabetes.[42] Stress hyperglycemia results from the acute metabolic and hormonal changes associated with the response to injury and stress.[43,44] Acute illness, surgery, and trauma raise levels of counterregulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone. This, in turn, results in a number of alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency.[45,46] The development of hyperglycemia leads to generation of reaction oxygen species (ROS), lipid peroxidation, and elevated inflammatory markers. It also increased pro-inflammatory cytokine such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1, which ultimately alter the immune system, [43,47-49] as well as altered hemostasis,

Version Date: 07/27/2016

increased platelet activation, adhesion and aggregation,[50] reduced plasma fibrinolytic activity and increased plasminogen activator inhibitor-1 (PAI-1) activity.[51]

Hospital Use of DPP-4 Inhibitors. We recently completed two randomized trials determined the safety and efficacy of treatment with sitagliptin alone or in combination with basal insulin in general medicine and surgery patients with T2D (see preliminary results).[22] In the first study, we demonstrated that the use of sitagliptin alone or in combination with basal insulin was well tolerated and resulted in no significant differences in daily BG, frequency of hypoglycemia or in the number of treatment failures compared to basal bolus regimen. DPP4 therapy is associated with low-risk of hypoglycemia, and these agents are ideal for the management of hyperglycemia and diabetes in the hospital setting. In a larger prospective, four-center randomized study in 280 patients we found that the use of sitagliptin plus a single dose of basal insulin (glargine) resulted in similar improvement in glucose control and complications, but in significant less insulin dosage and less number of injections compared to basal bolus regimen. These studies indicate that the use of sitagliptin is well tolerated and effective in maintaining good metabolic control avoiding or reducing insulin doses with low levels of hypoglycemia.
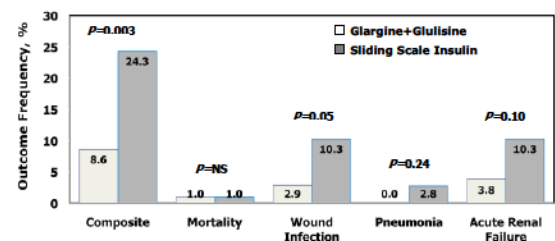
Significance and Innovation.
Approximately 30-40% of hospitalized patients will develop stress hyperglycemia.[2,23,24] Numerous studies have found that diabetes and hyperglycemia in non-DM patients are associated higher rates of complications and mortality.[12,30,31] There is increasing evidence indicates that stress hyperglycemia in non-DM patients is associated with worse clinical outcome compared to patients with a known history of DM.[2,10,11,13,32-34] Clinical guidelines recommend treating patients with hyperglycemia in the hospital with subcutaneous insulin protocols used in patients with DM,[52] but this can be labor intensive and costly. Furthermore, it is a retroactive approach and does not target prevention of hyperglycemia and the associated with increased risk of hypoglycemia. Our preliminary studies have shown that treatment with DPP4-inhibitors represent an alternative treatment to insulin therapy in improving glycemic control with low risk of hypoglycemia in a general inpatient population[22] and in preventing the need for subcutaneous insulin therapy after stopping CII in cardiac surgery patients with stress hyperglycemia. This proposal is an extension of previous work and will test whether 1) can stress hyperglycemia can be prevented or ameliorated with DPP4-inhibitors, and 2) can DPP4-inhibitors therapy, by preventing stress hyperglycemia lead to reduction in perioperative complications.

Preliminary Results
Our research team has extensive clinical and research experience in inpatient management of hyperglycemia and has published several RCTs in medical/surgery patients in ICU and non-ICU settings.[13,18,22,53-56]

RABBIT 2 Surgery Trial. This multicenter RCT compared the efficacy and safety of a basal/bolus regimen to sliding scale insulin (SSI) in non-ICU patients undergoing general surgery. Study outcomes included differences in daily BG levels and a composite of hospital complications including postoperative wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. A total of 211 patients were randomized to glargine once daily + glulisine before meals or to SSI given 4 times/day. The mean daily glucose concentration after the 1st day of basal bolus and SSI was 145±32 mg/dl and 172±47 mg/dl, respectively, p<0.01.

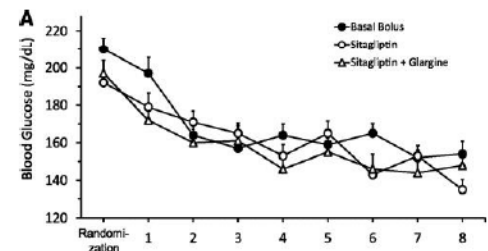
Fig 1. Rabbit Surgery: Surgical Complications

* Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

Umpierrez et al, Diabetes Care 34 (2):1–6, 2011

There were reductions with basal bolus as compared with SSI in the composite outcome (24.3% and 8.6%, OR: 3.39 (95% CI: 1.50-7.65); p=0.003). SSI had higher number of wound infection (2.9% vs. 10.3%), pneumonia (0% vs. 2.8%), and acute renal failure (3.8% vs. 10.3%) than basal bolus regimen. In addition, SSI treatment had higher number of post-surgery ICU admissions (12.5% vs. 19.6%, p=0.159) and ICU length of stay (1.2±0.6 vs. 3.2±2 days, p=0.003). We concluded that treatment with basal bolus improved glycemic control and reduced hospital complications compared to SSI in surgery patients with T2DM.
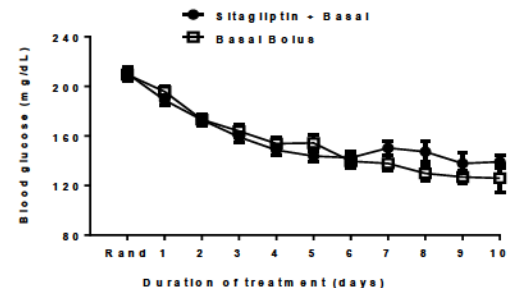
Sitagliptin Inpatient Pilot Study.[22]   In a two-center open label randomized pilot trial we recently determined differences in glycemic control between sitagliptin alone or in combination with basal insulin and basal bolus regimen in medicine and surgery patients with T2D. In this study, 90 patients with a BG between 140-400 mg/dl treated with diet, OAD or low-dose insulin ($\leq$ 0.4 U/kg/day) were randomized to sitagliptin once daily (n=30), sitagliptin and basal insulin (n=30) or to a basal bolus (n=30) regimen. Patients in the sitagliptin group received a daily dose of 100 mg or 50 mg as per renal function. Those in the sitagliptin plus glargine received sitagliptin and glargine starting at 0.25 U/kg once daily. Patients in the basal bolus group were started at 0.5 U/kg, given half as glargine once daily and half as lispro before meals. All groups received correction doses of lispro before meals and bedtime for BG >140 mg/dl. We found that treatment with sitagliptin alone or in combination with glargine resulted in similar glycemic control

Figure 2: Mean Daily BG during Treatment

compared to basal bolus regimen (Figure 2). There were no differences in mean daily BG, number of BG readings within target, hypoglycemia, frequency of treatment failures, hospital LOS or complications. In addition, treatment with sitagliptin had less daily insulin requirements and lower number of insulin injections, both, p<0.001. The study shows that use of a DPP4 inhibitor is a safe and effective for treatment of inpatient hyperglycemia.

We recently completed a second large, multi-center, prospective, open-label, randomized clinical trial to determine the safety and efficacy of sitagliptin plus basal insulin for the management of general medicine and surgery patients with T2D. 280 patients with T2D were included with (BG) ranging between 140-400 mg/dl. They were randomized to receive sitagliptin plus glargine once daily (SITA-GLA) or a basal bolus insulin regimen with daily glargine and rapid-acting insulin before meals (BB). There were no differences between treatment groups in the mean daily BG (170±49 vs. 169±48 mg/dl, p=0.96) (Figure 3), percentage of BG readings within target range of 70-180 mg/dl (57% vs. 60%, p=0.58), or in the number of patients with hypoglycemia (BG <70 mg/dl, 9% vs. 12%, p=0.45). None of the patients developed severe hypoglycemia. The number treatment failures (defined as more than 2 consecutive BG >240

Figure 3: Mean Daily BG during Treatment

mg/dl or a mean daily BG >240 mg/dl) were similar between SITA-GLA and BB groups (16% vs. 19%, p=0.54), as were the number of hospital complications of acute kidney injury, wound infection, stroke, acute myocardial infarction, respiratory failure, reoperation, or pneumonia (9% vs. 7%, p=0.52). There were also no differences in length of stay [median (IQR): 4 (3-8) vs. 4 (3-8) days, p=0.54]. The total daily insulin dose was significantly lower in the SITA-GLA group (0.23±0.14 vs. 0.33±0.16 U/kg) as were the number of daily insulin injections (2.2±1.0 vs. 2.9±0.9), both p<0.001.

GLUCO-CABG TRIAL[18]

This randomized controlled trial aimed to determine whether intensive BG control (intensive, target: 100-140 mg/dl) reduces perioperative complications compared to conservative BG control (conservative, 141-180 mg/dl) in hyperglycemic patients undergoing CABG. After ICU care, subjects were transitioned to a single treatment regimen targeting a BG<140 mg/dl before meals during the hospital stay and 90 days post discharge. The primary outcome was differences in a composite score of complications including mortality, wound infection, pneumonia,

Fig 4.

Composite of Complications in Stress Hyperglycemia (Non-DM) Treated to Intensive and Conservative targets!!

bacteremia, respiratory failure, acute renal failure, and major cardiovascular events. A total of 302 patients were randomized to intensive (n=151) or conservative (n=151) glucose control following a computerized insulin

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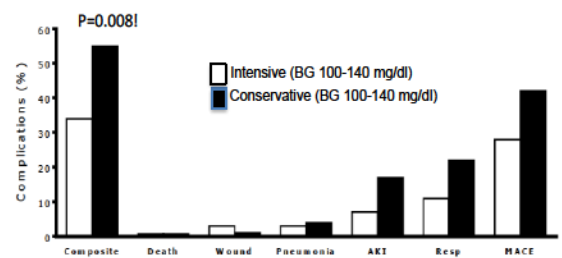
infusion algorithm. The mean ICU daily BG was 132±14 mg/dl (IQR 124-139) in the intensive and 154±20 mg/dl (IQR 142-164) in the conservative group (p<0.001). Overall, we observed a similar number of patients in the intensive and conservative groups experiencing ≥ 1 complications (42% vs. 52%, p=0.08). There were no differences in the composite or on individual complications in patients with DM; however, the composite of complications was lower in non-DM patients (stress hyperglycemia) in the intensive compared to the conservative group (p=0.008) (Figure 4).

In summary, during the past decade our group has provided novel and important information to guide health care providers in the hospital management of patients with hyperglycemia and diabetes. Our preliminary studies indicate that stress hyperglycemia is common and associated with increased rate of complications. The proposed studies will determine if DPP4 agents are effective in the prevention and management of stress hyperglycemia in patients undergoing non-cardiac surgery.

Version Date: 07/27/2016

METHODOLOGY

Aim: To determine whether treatment with sitagliptin once daily can prevent the development of stress hyperglycemia during the postoperative period in non-diabetic patients undergoing general surgery.

Rationale:

Approximately 30% of non-diabetic patients undergoing general non-cardiac surgery will develop stress hyperglycemia (BG > 140-180 mg/dl) and require treatment with insulin during the perioperative period.[6,14,57,58] Few trials have investigated the impact of hyperglycemia in general non-cardiac surgery patients.[2,12] The current standard of care according national medical associations is to treat stress hyperglycemia with insulin, with up to 4 injections per day.[52,59] This, however, is costly and requires significant nursing resources and is associated with up to 20-30% risk of hypoglycemia.[56,60] We have shown that a DPP-4 inhibitor can be used to reduce hyperglycemia safely and effectively in diabetic patients in the hospital with relatively low risk of hypoglycemia (preliminary results).[22] Our study aims to safely reduce the risk of developing postoperative hyperglycemia and associated complications with the use of a once daily oral medication.

METHODS:

This pilot randomized, placebo-controlled, intent-to-treat trial will be conducted in 100 subjects between 18-80 years of age, without a known history of diabetes and with normoglycemia [BG<126 mg/dl or random BG ≤ 140 mg/dl] undergoing non-cardiac surgery. Subjects will be consented either prior to hospitalization at the pre-operative clinic visit or during hospitalization before surgery. Subjects will be randomized to receive either sitagliptin or placebo starting one day prior to surgery and continued daily during hospitalization to determine if stress hyperglycemia, defined as a BG >140 mg/dL can be prevented or reduced with the use of a DPP4-inhibitor.

Treatment Groups:
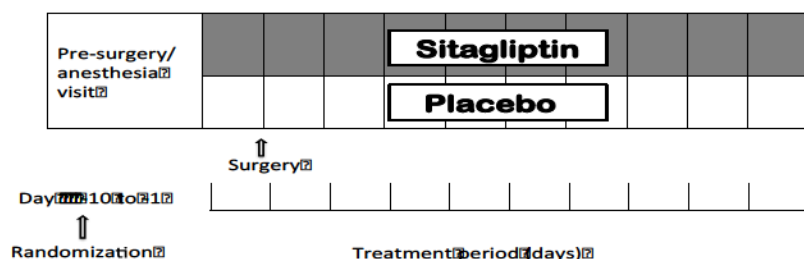
Primary outcome:

To determine whether treatment with sitagliptin once daily can prevent the development of stress hyperglycemia during the postoperative period in non-diabetic patients undergoing general surgery.

Secondary outcomes:

1. Total daily dose of insulin dose for patients requiring insulin
2. Length of hospital stay
3. Number of patients requiring SC insulin, either SSI or basal
4. Hypoglycemic events (BG < 70 mg/dl); severe hypoglycemia (BG < 40 mg/dl)
5. Transfer to the ICU (immediately after surgery or during hospitalization) and number of days in the ICU
6. Hospital readmission and Emergency room visit after discharge.
7. Individual and composite of the following complications:
   - Wound infection
   - Respiratory failure
   - Pneumonia
   - Acute kidney injury (defined by increase in creatinine by 0.5 meq/L above preoperative value)
   - Major adverse cardiac events

Version Date: 07/27/2016

- Bacterial septic infection
- Death

Study population: *Patients between 18-80 years of age, without a known history of diabetes* and with normoglycemia [fasting BG<126 mg/dl dl or random BG ≤ 140 mg/dl] *planned for non-cardiac surgery will undergo screening at their preoperative clinic visit or during hospitalization prior to surgery.*

The screening and recruitment will occur in 2 different scenarios. For patients who undergo pre-anesthesia and surgery screening (elective cases) will be screened for inclusion/exclusion criteria and will be invited to participate by a study coordinator and/or investigator. If accepted to participate, the patient will be given a sitagliptin or placebo tablet and instructed to take the medication the day before and the day of surgery (see graph in page 6).

For hospitalized patients without pre-anesthesia visit, which we anticipate will be about half of the patients, we will approach and invite to participate if no history of diabetes and with a fasting BG < 126 mg/dL or random BG ≤ 140 mg/dL.

Inclusion criteria:
1. Men and women between the ages of 18 and 80 years undergoing non-cardiac surgery.
2. No previous history of diabetes or hyperglycemia
3. Randomization fasting BG <126 mg/dl or random ≤ 140 mg/dl.

Exclusion criteria:
1. Patients with hyperglycemia (fasting BG ≥ 126 or random BG >140mg/dl)
2. Patients with prior history of diabetes with HbA1c ≥ 6.5% or previous treatment with oral antidiabetic agents or insulin.
3. Patients undergoing cardiac surgery.
4. Patients anticipated to require ICU care following surgery.
5. Severely impaired renal function (GFR < 30 ml/min) or clinically significant hepatic failure.
6. Moribund patients and those at imminent risk of death (brain death or cardiac standstill).
7. Subjects with gastrointestinal obstruction or adynamic ileus or those expected to require gastrointestinal suction.
8. Patients with clinically relevant pancreatic or gallbladder disease.
9. Treatment with oral (equivalent to prednisone> 5 mg/day) or injectable corticosteroid.
10. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study
11. Pregnancy or breast-feeding at time of enrollment.

Procedures
A total of 100 patients will be consented during their surgery clinic visit or during hospitalization.
Medication:
- The study drug (sitagliptin or placebo) will be started one day prior to surgery and continued once daily in a blinded fashion for up to 8 days postoperatively.
- Patients with normal renal function will receive two 50 mg tablets sitagliptin (total of 100 mg) or two placebo tablets.
- Patients with GFR of <50 ml/min will receive one 50 mg tablet of stiagliptin (total of 50 mg) or one placebo tablet.
- If a patient's GFR changes during hospitalization, the dose of sitagliptin will be adjusted accordingly. If GFR is ≥ 50mL/min, the dose will be 100 mg; If GFR is <50 and ≥30 mL/min, the dose will be adjusted to 50 mg; if the GFR decreases to <30, the dose will be changed to 20 mg.
- During hospitalization after surgery, patients will have point of care (POC) testing done 4 times daily; for patients who are eating, POC testing will be done before meals and at bedtime; for patients not eating (NPO),

POC testing will be every 6 hours. One blood glucose check will also be done during surgery to assess predictive value of intraoperative hyperglycemia in developing sustained hyperglycemia postoperatively.

- Patients who develop hyperglycemia during surgery or in the recovery unit, will be treated with insulin as per institution protocol (standard of care).
- Patients with fasting and/or premeal BG >180 mg/dl will receive coverage with sliding scale insulin (supplements). Those with 2 consecutive fasting and/or premeal BG >180 mg/dl, or with average daily BG >180 mg/dl will be started on rescue therapy with SC detemir or glargine insulin once daily plus correction doses by sliding scale. [55]

Supplemental (correction) insulin. Supplemental (lispro or aspart) insulin will be administered following standard "sliding scale" protocol outlined below.

Supplemental Sliding Scale Insulin (number of units) - administer dose before meals.

Blood Glucose (mg/dL)	☐ Sensitive	☐ Usual	☐ Resistant
181-220	2	3	4
221-260	3	4	5
261-300	4	5	6
301-350	5	6	7
351-400	6	7	8
> 400	7	8	9

** Check appropriate column below and cross out other columns

At bedtime, give according to Bedtime Supplemental Sliding Scale Insulin starting at BG >220 mg/dl:

Blood Glucose (mg/dL)	☐ Sensitive	☐ Usual	☐ Resistant
221-260	1	2	3
261-300	2	3	4
301-350	3	4	5
351-400	4	5	6
> 400	5	6	7

** Check appropriate column below and cross out other columns

The numbers in each column indicate the number of units of aspart or lispro insulin per dose. If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal following the "usual" column dose. Supplemental insulin at bedtime = half of premeal insulin dose at BG > 220 mg/dl. If a patient is not able to eat (NPO), supplemental insulin will be administered every 6 hours (6-12-6-12) following the "sensitive" column dose.

Initiation of subcutaneous insulin

Patients with fasting and/or premeal BG >180 mg/dl will receive coverage with sliding scale insulin (supplements). Those with 2 consecutive fasting and/or premeal BG >180 mg/dl or with average daily BG >180 mg/dl, will be started on detemir or glargine insulin once daily as basal plus correction or on basal bolus insulin regimen plus supplements with rapid-acting insulin analog. The study drug-sitagliptin or placebo will be continued once daily in all patients independently of the need for insulin therapy.

Basal insulin therapy with Detemir or Glargine:
- Continue study drug (sitagliptin or placebo) once daily.

- Patients with averageBG between >180 mg/dL= start detemir or glargine at 0.2 units per kg weight per day.
- Patients with GFR <50 or over the age of 70= start detemir or glargine at 0.1 units per kg weight per day.
- Basal insulin will be given once daily, at the same time of day.

Insulin adjustment. The total detemir or glargine daily insulin dose will be adjusted as follow:
- Fasting and pre-meal BG between 100-180 mg/dl without hypoglycemia the previous day: no change
- Fasting and pre-meal BG between >180-240 mg/dl: increase detemir or glargine dose by 10% every day
- Fasting and pre-meal BG >241 mg/dl: increase detemir or glargine dose by 20% every day
- Fasting and pre-meal BG <100 mg/dl: reduce detemir or glargine by 20% or stop if patient is already on less than 0.1 units/kg of body weight

Data collection and data entry. The study coordinators will enter baseline and daily data for this study into data collection paper forms and into an electronic database provided by the Emory Research Information Technology Department. Baseline data will include demographics/history form (subject gender, date of birth, ethnicity, dates of hospitalization and operation, history of diabetes, type of treatment of diabetes and comorbid conditions, body weight, BMI, type of surgery. Daily information will be collected on treatment (insulin dosage, antibiotics), nutrition support, BG and laboratory values, hospital complications and adverse events, and length of ICU and hospital stay.

STATISTICAL ANALYSIS

To determine whether treatment with sitagliptin once daily can prevent the development of stress hyperglycemia during the postoperative period in non-diabetic patients undergoing general surgery.

Analysis of Primary Endpoint: The primary endpoints in this study are to determine differences between sitagliptin and placebo treatment on the frequency of stress hyperglycemia during surgery who require therapy with SC insulin. We will first use two-sided Chi-square test or Fisher's exact test to compare primary endpoints between treatment groups. Next, we will perform multivariate logistic regression to estimate the difference in the occurrence rate of the primary endpoint while adjusting for other relevant covariates such as age and gender. 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 predictive model.

Sample Size Calculation and Power Analysis:
We have performed sample size and power calculations based on our preliminary data on retrospective chart review, which showed that 29% of non-DM patients develop stress hyperglycemia following general surgery. We anticipate that sitagliptin will reduce the rate of hyperglycemia by 50-80% (corresponding to odds ratio (OR) in the range of 0.42-0.15). We calculate the sample size based on the OR estimate of 0.42 and provide the power for the larger treatment effects represented by OR=0.42, 0.3, 0.2, 0.15 (see Table). More specifically, conservatively using two-sided Fisher's exact test, two-sided, with alpha=0.05, the sample size required for 80% power to detect the conjectured treatment effect of OR=0.42 (ie. 29.0% vs 14.5%) would be 143 patients per study group. Accounting for 15-20% attrition rate, recruiting 179 patients will need to be recruited in each group. A total of 358 patients (179 patients per group) will need to be recruited. In this pilot study, we will recruit a total of 100 patients (50 per group).

Table. Power computed based on two-sided Fisher's exact test with alpha=0.05 and sample, 143 per group

Effect Size: Odds ratio	0.42	0.3	0.2	0.15
Primary endpoint: Stress hyperglycemia in the hospital				
Event rates	29% vs. 14.5%	29% vs. 10.9%	29% vs. 7.6%	29% vs. 5.8%

Version Date: 07/27/2016

| Power | 80.2% | 96.1% | 99.6% | 99.9% |

Analysis of Secondary Endpoints: The secondary outcomes of interest can be a binary outcome (eg. indicator for whether patients require transfer to the ICU), or a count outcome (eg. number of perioperative complications), or a continuous outcome (eg. mean daily BG concentration). We will adopt the same strategy proposed for the primary endpoint to analyze any binary secondary outcomes. For secondary endpoints measured as counts, we plan to use nonparametric tests such as Krustal-Wallis tests to compare them between the two study groups. Univariate Poisson regression (or Negative Binomial regression) will be performed to estimate the marginal treatment effect. In addition, we will also conduct multivariate Poisson regression (or Negative Binomial regression) to assess the outcome differences between the two study groups with potential confounders taken into account. For secondary endpoints, which produce continuous outcomes, we will use two-sample t-tests or nonparametric Wilcoxon tests to compare them between the two study groups. Transformations will be applied if normality violation is detected. Multivariate linear regression will be further conducted to assess the difference in continuous secondary outcomes between the two groups while accounting for other potential confounders. We will use standard model selection and model checking procedures for Poisson regression (or Negative Binomial regression) and linear regression to decide the final models and assess their fits to the data.

Data and Safety Monitoring Plan (DSMP): The Data and Safety Monitoring Plan (DSMP) will include 2 independent reviewers monitor on safety, treatment compliance, and evaluate the efficacy of the intervention being studied in this clinical trial. The DSMP will meet at 6-month intervals and report on study progress to the IRB.

Interim Analysis and Stopping Rules: We plan to perform one interim analysis on the primary endpoint every 6 months and when half of the subjects have been randomized. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in hospital complications (two-sided alpha level, <0.01) between the treatment groups.

Future direction
Using the pilot data collected from the proposed pilot study, I plan to develop a large-randomized-controlled trial investigating whether stress hyperglycemia and associated complications can be prevented.

HUMAN SUBJECTS

Inform consent and randomization: All patients scheduled to undergo surgery will be considered potential candidates in this study. Patients will be consented during the preoperative clinic evaluation or on admission to the surgical service at least 24 hours prior to scheduled surgery. The investigators or study coordinators will review and explain the contents of the informed consent document to the eligible patient. The potential subject will be informed of the purpose of the study, the randomization procedure, and the risks and benefits of participation. The potential subject will also be informed that he/she may refuse to participate, and that even if he/she consents to participate he/she may withdraw from the study at any time.

Study Site: This pilot study will be conducted at Emory University Hospital and Grady Memorial Hospital, Atlanta.

Version Date: 07/27/2016

Risk associated with participation:

Hypoglycemia: Hypoglycemia is the main adverse event and safety issue in the study. In our previous surgery study, we observed that mild (BG ≤70 mg/dL) hypoglycemia occurred in 20-30% and severe (BG ≤40 mg/dL) hypoglycemia occurred in 3-4% of patients treated with SC insulin.[60] The use of insulin in combination with DPP4 inhibitors may increase the risk of hypoglycemia during the hospital stay. The number of mild and severe hypoglycemia and clinical consequences (neurological and cardiovascular) will be compared across treatment arms.

Treatment of hypoglycemia: Hypoglycemia, defined as a BG <70 mg/dL will be treated by a standard hypoglycemia protocol available at the institution. In brief, Hypoglycemia, for BG < 70 mg/dL and patient is alert and can tolerate oral intake, give 20 grams of fast-acting carbohydrate (6 oz. fruit juice or regular soda, crackers); if patient is not alert and cannot tolerate oral intake, give 1ampule (50 mL) of D50. Check finger stick BG q 15 minutes and repeat above treatment until BG > 100 mg/dL. Once BG > 100 mg/dL, repeat finger stick BG 1 hour later and treat as follows: If BG < 70 mg/dL, call MD and follow hypoglycemia orders (above); if BG 70 – 100 mg/dL, give snack/scheduled meal and check BG q1 h until BG >100 mg/dl; if BG > 100, no further treatment needed.

Hyperglycemia: It is possible that following the proposed protocol, patients randomized to the conventional treatment arm may develop higher numbers of hyperglycemic events (BG 180 mg/dl) which may lead to increased risk of complications. We expect that ~20% of subjects will experience one or more episodes of hyperglycemia. The frequency of severe hyperglycemia will be analyzed statistically.

Protection against risks: Our strict inclusion and exclusion criteria for entry will help to minimize risks. In addition, we will carefully monitor capillary BG at the bedside using the hospital certified meter, b) only experienced nurses/or phlebotomist will draw blood samples, and c) no patients with history of significant pancreatic, renal or hepatic failure will be recruited in this study, d) study subjects will receive rescue therapy with insulin in the event of hyperglycemia.

Potential benefits to the subject: We believe that all subjects will benefit from this study. Intensified blood glucose monitoring and blood glucose control has been shown to significantly reduce hospital complications associated with hyperglycemia and hypoglycemia.

Inclusion of women: We anticipate that ~50% of the study subjects will be female. No patients under the age of 18 and no pregnant women will be included in the study.

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

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

Confidentiality: Informed consent will follow the procedure of Emory University Institutional Review Board. Every participant will be informed in writing and verbally with the important and key points of the study. The investigators or the research coordinators will obtain a witnessed informed consent prior to inclusion into the study. Data collection records with personal identifiers will be stored in locked file cabinets. All data maintained in the computerized database will be accessible only with a login and protected password. After the study is completed, all data will be kept in a locked file. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects.

Version Date: 07/27/2016

Payment for participation: Participation in this study is voluntary. Patients will receive fifty ($50) at the time of hospital discharge for participation in the study. If a participant should stop participation before completion, they will receive twenty five ($25.00) at the time of termination.

Financial conflict of interests.   None of the investigators in this study have any activities that may represent a conflict of interest. None of the investigators have an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

Time Line: We anticipate completion of enrollment in the pilot study within 1 year with about 6 patients enrolled per month.

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Version Date: 07/27/2016