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**Sitagliptin for the Prevention and Treatment of Hyperglycemia in Patients with Type 2 Diabetes  
Undergoing Cardiac Surgery (SITA-CABG DM TRIAL)**

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# **Sitagliptin for the Prevention and Treatment of Hyperglycemia in Patients with Type 2 Diabetes Undergoing Cardiac Surgery (SITA-CABG DM TRIAL)**

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## I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

More than 500,000 patients undergo coronary artery bypass graft surgery (CABG) each year in the United States.<sup>1</sup> Nearly 30% to 40% of patients undergoing cardiac surgery have diabetes mellitus (DM).<sup>2,3</sup> More than 90% of patients with DM and ~80% of patients without DM will develop hyperglycemia (defined as a BG >140 mg/dl) after surgery.<sup>4-7</sup> Several cohort studies have reported that hyperglycemia; in patients with and without DM, is an independent risk factor of morbidity and mortality after cardiac surgery.<sup>8-12</sup> Patients with DM have higher rates of deep sternal wound infections,<sup>11,13</sup> acute renal failure,<sup>6</sup> longer hospital stay,<sup>9,14</sup> and perioperative mortality<sup>14,15</sup> when compared to those without DM. Despite ongoing debate about the optimal glucose target, there is strong agreement that improvement in glycemic control reduces complications and inpatient mortality.<sup>16-18</sup> In the GLUCO-CABG trial,<sup>19</sup> we reported lower, but not significant differences in a composite of complications between intensive and conservative regimens in patients with DM; however, we observed a reduction in hospital complications in non-DM patients with stress hyperglycemia treated with intensive glucose control (see preliminary results).

Clinical guidelines from professional organizations recommend treatment with continuous intravenous insulin infusion (CII) for treatment of hyperglycemia in cardiac surgery patients with DM and hyperglycemia.<sup>7,20-22</sup> Although effective and widely utilized<sup>16,18,23</sup>, the use of CII is labor intensive, requiring hourly BG testing and insulin drip adjustment, and is associated with a significant risk of hypoglycemia, reported in 5 – 32% of patients in the ICU.<sup>24-27</sup> Hypoglycemia after cardiac surgery has been independently associated with increased risk of complications, longer length of hospital stay, and increased mortality.<sup>28-30</sup> Recently, the inpatient therapy with dipeptidyl peptidase-4 [DPP-4] inhibitors has been shown to be an effective alternative to insulin therapy in improving glycemic control with low risk of hypoglycemia.<sup>31</sup> In addition, our preliminary studies indicate that the use of sitagliptin is effective in maintaining glucose control and in preventing the need for subcutaneous insulin therapy during the transition period from the ICU to regular floors in cardiac surgery patients with stress hyperglycemia (see preliminary data).

We hypothesize that treatment with sitagliptin (Januvia®), by reducing glucagon-mediated hepatic glucose production and by stimulating insulin secretion in a glucose-dependent fashion, will prove to be a safe and effective for the prevention and treatment of hyperglycemia during the perioperative period in cardiac surgery patients with type 2 diabetes.

### I.1. Specific Aims

**Aim 1. To determine whether treatment with sitagliptin reduces the frequency and severity of hyperglycemia and need for CII in the ICU compared to placebo in patients with type 2 diabetes undergoing CABG surgery.** In this prospective, randomized, blinded, placebo-controlled study, patients with type 2 diabetes (T2D) treated with diet, oral antidiabetic drugs (OADs), and/or insulin will be randomized to receive sitagliptin or placebo starting the day prior to surgery and continue once daily in the ICU.

**Hypothesis:** Treatment with sitagliptin will significantly reduce the severity of hyperglycemia and the need for CII during the perioperative period in T2D patients undergoing CABG.

**Aim 2. To determine whether treatment with sitagliptin is effective in maintaining glycemic control and in preventing the need for subcutaneous (SC) insulin therapy in patients with T2D during the transition from ICU to telemetry unit in patients with T2D undergoing CABG.** In this study, patients randomized to sitagliptin or placebo in Aim 1 will continue treatment after transition from ICU to regular wards.

**Hypothesis:** Treatment with sitagliptin will be effective in maintaining glucose control avoiding the need for SC insulin therapy after transition from ICU to regular wards in T2D undergoing CABG surgery.

### I.2. Overall Design and Study Interventions

This prospective, randomized, blinded pilot clinical trial will be conducted in patients with T2D undergoing CABG surgery. Subjects will be consented prior to surgery at the surgery-anesthesia pre-hospitalization assessment or on admission to the hospital. Subjects will be randomized to receive sitagliptin or placebo starting one day prior to surgery and continued daily in the ICU (Aim 1) to determine if hyperglycemia (BG > 180 mg/dl

in the ICU) could be prevented or ameliorated with the use of a DPP4-inhibitor. Treatment with sitagliptin or placebo (Aim 2) will be continued during transition to regular floors to confirm our preliminary data that treatment with DPP4-inhibitors facilitates the management of hyperglycemia avoiding the use of SC insulin after stopping insulin infusion. Study patients who develop hyperglycemia during the hospital stay (BG > 180 mg/dl in non-ICU areas) will be managed following our institution standard insulin protocols.

The dose of study drug will depend on the patient's GFR at time of randomization. Patients with a calculated  $\text{GFR} \geq 50 \text{ mL/min/1.73m}^2$  will receive study drug 100mg daily. Patients with calculated GFR between 30-49  $\text{mL/min/1.73m}^2$  will receive study drug 50mg daily. If the calculated GFR drops below 30  $\text{mL/min/1.73m}^2$ , patients will receive study drug 25mg daily. If the calculated GFR changes after randomization, study drug will be adjusted accordingly.

### **I.3. Background and Significance**

**I.3.1. Diabetes and Coronary Heart Disease.** The prevalence of diabetes mellitus is rising at an alarming rate and it currently affects ~200 million people worldwide and 29 million in the United States.<sup>32</sup> The adverse microvascular and macrovascular consequences of diabetes are well recognized, as is the accompanying accelerated rate of atherosclerosis that predisposes patients to coronary artery disease and to higher rates of myocardial infarction and death.<sup>33-35</sup> Coronary heart disease causes much of the serious morbidity and mortality in patients with diabetes, who have a 2- to 4-fold increased risk of myocardial infarction,<sup>36,37</sup> and 3 times as many deaths as people without diabetes.<sup>33,38</sup>

**I.3.2. Diabetes and CABG surgery.** More than 500,000 patients undergo CABG surgery each year in the United States.<sup>1</sup> The national prevalence of diabetes among patients undergoing CABG is about 30%.<sup>39-41</sup> Patients with diabetes who undergo CABG surgery have increased perioperative mortality and morbidity and more recurrent episodes of angina.<sup>3,9,17,42</sup> Similarly, long-term survival after surgical revascularization is significantly reduced in diabetics compared to nondiabetic subjects.<sup>43,44</sup> In the BARI trial, diabetics had significantly lower 5-year survival rates (73.3% vs. 91.3%) than nondiabetic subjects.<sup>45</sup> Most deaths after CABG are attributable to cardiac causes in ~ two-thirds of patients (ischemia due to graft failure, left ventricular failure and dysrhythmia),<sup>11,41,46,47</sup> as well as increased neurologic complications,<sup>48</sup> renal dysfunction,<sup>49</sup> and infectious complications.<sup>11,50</sup>

**I.3.3. Glycemic control in cardiac surgery patients with T2D and Hyperglycemia.** Hyperglycemia during the perioperative period is reported in >90% of patients with T2D and in ~80% of patients without a history of DM.<sup>4-6</sup> Large cohort studies have identified hyperglycemia, in patients with and without DM as an independent risk factor of poor outcome after cardiac surgery compared to patients with normoglycemia, specifically higher perioperative mortality,<sup>14,15</sup> deep sternal wound infections,<sup>11,13</sup> renal failure,<sup>6</sup> postoperative strokes,<sup>9,51</sup> longer hospital stays,<sup>9,14</sup> and higher health care resource utilization.<sup>52-54</sup>

The results of several clinical trials in critically ill and surgery patients indicate that improvement of glycemic control reduces length of stay (LOS), risk of multi-organ failure and systemic infections,<sup>13,16,23</sup> as well as mortality in patients with stress hyperglycemia and diabetes.<sup>16,55</sup> The Portland Diabetic Project, a prospective, non-randomized study of diabetic patients who underwent CABG<sup>13</sup> reported that the use of 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%.<sup>56</sup> The Leuven trial,<sup>16</sup> a prospective RCT of intensive insulin therapy in diabetic and non-diabetic surgical ICU patients treated to target glucose between 80 and 110 mg/dl reduced hospital mortality by 34%. A subgroup analysis by Van den Berghe et al<sup>57</sup> 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. Similarly, in the GLUCO-CABG trial (see preliminary results) we found a lower, but non-significant reduction 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.<sup>19</sup>

**1.3.4. Stress hyperglycemia: mechanisms and consequences.** The ADA/AACE and Endocrine Society guidelines on inpatient hyperglycemia defined hyperglycemia or hospital-related hyperglycemia as any BG concentration >140-180 mg/dl. Acute illness, surgery, and trauma raise levels of counterregulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone. The counterregulatory response results in a number of alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency.<sup>58,59</sup> 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- $\alpha$ ), interleukin (IL)-6, and IL-1, which ultimately alter the immune system,<sup>60-63</sup> as well altered hemostasis, increased platelet activation, adhesion and aggregation,<sup>64</sup> reduced plasma fibrinolytic activity and increased plasminogen activator inhibitor-1 (PAI-1) activity.<sup>65</sup>

**1.3.5. Hospital Use of DPP-4 Inhibitors.** We recently completed a randomized two-center open label pilot trial determined the safety and efficacy of treatment with sitagliptin alone or in combination with basal insulin in general medicine and surgery patients with T2D.<sup>31</sup> In this pilot study, 90 general medicine and surgery patients with a BG between 140-400 mg/dl treated with diet, oral antidiabetic drugs or low-dose insulin were randomized to sitagliptin once daily, sitagliptin and basal insulin, or basal bolus insulin. All groups received correction doses of lispro before meals and bedtime for BG >140 mg/dl. Patients in the sitagliptin group received a single daily dose of 50-100 mg based on kidney function. 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 different uncontrolled pilot trial we treated a group of 22 patients with stress hyperglycemia requiring insulin infusion in the ICU with sitagliptin. Patients were treated with sitagliptin 100 mg/day at discontinuation of CII (as an alternative to the SQ insulin) and at transition to regular floor. The use of sitagliptin was well tolerated and patients remained in good metabolic control avoiding transition to SQ insulin after discontinuation of IV insulin drip (see preliminary results).

### **1.3.6. Significance and Innovation.**

**Significance.** Most cardiac surgery patients, with or without history of T2D, develop significant hyperglycemia and require CII during the perioperative period.<sup>6,16,66</sup> There is strong evidence to indicate that hyperglycemia is an independent risk factor of morbidity and mortality after cardiac surgery.<sup>8-12</sup> Clinical guidelines recommend treating patients with hyperglycemia with CII in the ICU;<sup>7,20,21</sup> however, CII is labor intensive, costly, and associated with a high rate of hypoglycemia (5–32%).<sup>24-27</sup> Hypoglycemia after cardiac surgery has been independently associated with increased risk of complications and mortality<sup>28-30</sup>. The concerns regarding complications associated with insulin therapy has led to the search of alternative treatment regimens. 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<sup>31</sup> and in preventing the need for subcutaneous insulin therapy after stopping CII in cardiac surgery patients with stress hyperglycemia.

**Innovation.** This proposal will test 2 major innovative areas: 1) can hyperglycemia, which is present in more than 90% of patients with T2D after CABG surgery, be prevented or ameliorated with the use of a DPP4-inhibitors? And 2) can DPP4-inhibitors facilitate the management of patients with T2D avoiding the use of subcutaneous basal bolus insulin therapy during the transition from ICU to regular floors? These are two important clinical questions that may facilitate care of millions of patients with T2D undergoing cardiac surgery. More importantly, if treatment with sitagliptin is proven effective in reducing the severity of hyperglycemia during the perioperative period, and in reducing the rate of hyperglycemia and hypoglycemia during the transition from ICU to regular wards, it is possible that these agents will reduce the number of perioperative complications in patients with T2D undergoing CABG surgery.

## 2. PRELIMINARY RESULTS:

Our research team has extensive clinical and research experience in inpatient management of hyperglycemia and has published several randomized controlled trials in medical/surgery patients in ICU and non-ICU settings.<sup>19,31,67-</sup>

<sup>71</sup> Emory University and affiliated hospitals serve as cardiovascular referral center including cardiac surgery to a large population based in the city of Atlanta and the state of Georgia. More than 1000 major CV surgeries (CABG, aortic and valve surgery) procedures are performed every year at the 3 participating institutions (Emory University, Midtown Hospital and Grady Hospital).

### 2.1. RABBIT 2 Surgery Trial.

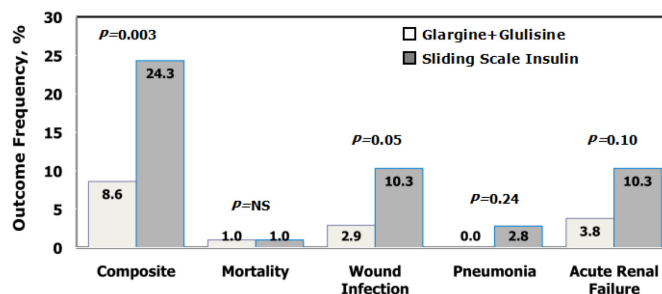
This multicenter RCT compared the efficacy and safety of a basal/bolus regimen to sliding scale insulin (SSI) in non-ICU patients undergoing general surgery. Study outcomes included differences in daily BG levels and a composite of hospital complications including postoperative wound infection, pneumonia, 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,  $p < 0.01$ . 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. We concluded that treatment with basal bolus improved glycemic control and reduced hospital complications compared to SSI in surgery patients with T2D.

**2.2. Sitagliptin Inpatient Pilot Study.**<sup>31</sup> 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 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.

### 2.3. GLUCO-CABG TRIAL<sup>19</sup>

This randomized controlled trial aimed to determine whether intensive BG control (intensive, target: 100-140 mg/dl) reduces perioperative complications compared to

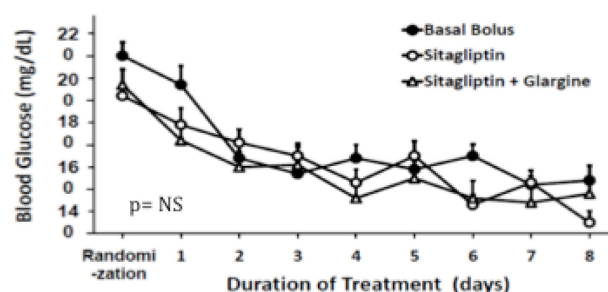
**Fig 1. Rabbit Surgery: Surgical Complications**



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

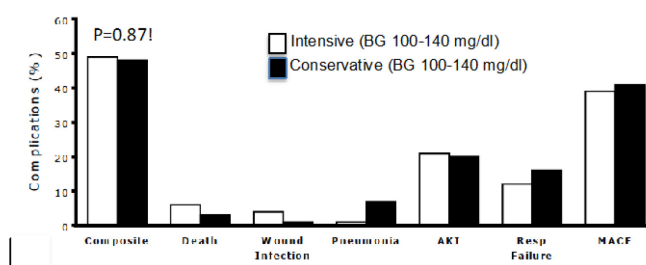
Umperetz et al, Diabetes Care 34 (2):1-6, 2011

**Fig 2 Mean Daily BG During Treatment**



**Fig 3.**

**Composite of Perioperative Complications in DM Patients Treated to Intensive and Conservative Glucose targets!!**

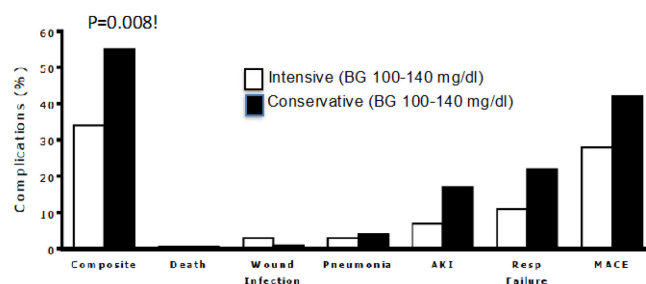




conservative BG control (conservative, 141-180 mg/dl) in hyperglycemic patients undergoing CABG. After ICU care, subjects were transitioned to a single treatment regimen targeting a BG<140 mg/dl before meals during the hospital stay and 90 days post discharge. The primary outcome was differences in a composite score of complications including mortality, wound infection, pneumonia, 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 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  $\geq 1$  complications (42% vs. 52%,  $p=0.08$ ). There were no differences in the composite or on individual complications in patients with DM (Figure 3); however, the composite of complications was lower in non-DM patients with stress hyperglycemia (Fig 4) in the intensive compared to the conservative group ( $p=0.008$ ).

Fig 4.

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

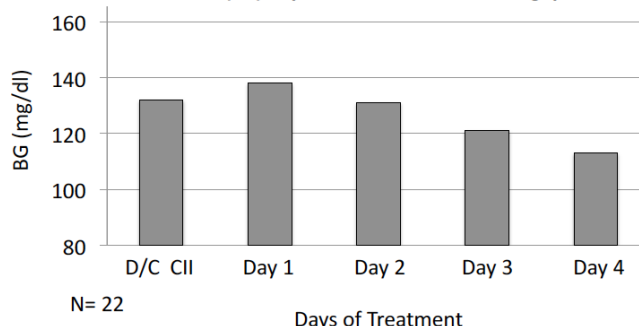


## 2.4. Sitagliptin after discontinuation of CII in patients with stress hyperglycemia.

In an uncontrolled open label pilot study, we treated a group of 22 non-DM patients with stress hyperglycemia in the ICU with sitagliptin 100 mg/day at discontinuation of CII (as an alternative to the standard SQ insulin) and at transition to regular floor (Fig. 5). The use of sitagliptin was well tolerated and patients remained in good control with a mean daily BG < 140 mg/dl during days 1 and 4 after transition to regular floor. The sitagliptin therapy was discontinued the day before discharge and all patients were successfully discharged home without insulin injections.

Fig 5

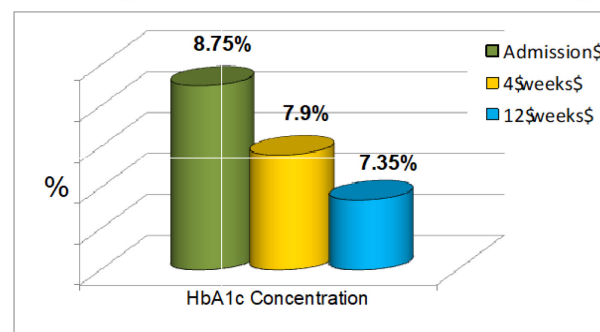
**BG levels after discontinuation of continuous insulin infusion (CII) in patients treated with sitagliptin**



**Transition of Care after Discharge.** In a recent preliminary study we assessed the efficacy of an HbA1c based algorithm for the management of 224 non-ICU patients with T2D (Fig. 6). Patients with an admission HbA1c < 7% were discharged on their same outpatient antidiabetic regimen (OADs and/or insulin). Patients with an HbA1c between 7% and 9% will be discharged on a combination of OADs and basal (glargine) insulin at 50% of total daily hospital dose. Patients with an admission HbA1c  $\geq 9\%$  were discharged on a combination of oral agents and basal insulin at 80-100% of total daily hospital dose or on a basal bolus regimen at the same hospital dosage. The admission HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge ( $p<0.01$ ). We concluded that the admission HbA1c concentration is beneficial in designing the discharge treatment algorithm after discharge in patients with T2D.

Fig 6

**Change in HbA1C levels after discharge**



Umpierrez et al. Diabetes Care 2014

**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 hyperglycemia is common and associated with increased rate of complications in medicine and surgery patients with T2D. The proposed studies will determine if DPP4 agents are effective in the prevention and management of hyperglycemia in patients with T2D undergoing CABG surgery.

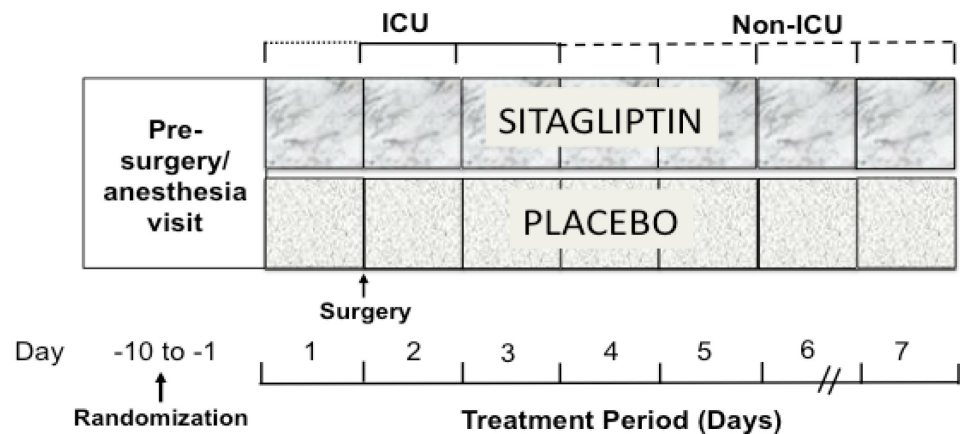
### 3. EXPERIMENTAL PLAN.

**3.1. Rationale:** More than 90% of patients with T2D undergoing cardiac surgery will develop hyperglycemia (BG>140-180 mg/dl) and require treatment with CII during the perioperative period.<sup>6,7,16,66</sup> There is strong evidence to indicate that hyperglycemia is an independent risk factor of morbidity and mortality after cardiac surgery.<sup>8-12</sup> Clinical guidelines recommend treatment with intravenous insulin infusion (CII)<sup>7,20,21</sup>, that is labor intensive, costly, and associated with increased risk of hypoglycemia<sup>24-27</sup>. The rate of severe hypoglycemia (BG < 40 mg/dl) in the ICU after cardiac surgery has ranged between 5% and 19% in previous clinical trials.<sup>16,17,26,72</sup> Most patients with T2D who are treated with CII in the ICU require transition to SC insulin (basal or basal bolus approach) when transferred to regular wards<sup>19,73</sup>. In such patients, daily insulin dose adjustments are needed to prevent hypoglycemia once the stress abates 2 to 5 days after surgery. The basal bolus approach is labor intensive requiring multiple injections per day and is associated significant risk of hypoglycemia reported in 10% to 30% of patients in non-ICU setting.<sup>68,71,74-76</sup> Hypoglycemia after cardiac surgery has been independently associated with increased risk of complications and increased mortality.<sup>28-30</sup> Our preliminary studies indicate that the use of sitagliptin is effective in achieving glucose control in patients with T2D,<sup>31</sup> and in preventing the need for SC insulin therapy after stopping CII in cardiac surgery patients with hyperglycemia.

### 3.2. STUDY DESIGN and METHODS

This randomized, placebo-controlled, intent-to-treat trial will include subjects between 18-80 years of age, with a history of T2D undergoing CABG surgery. Patients with T2D treated with diet, oral antidiabetic drugs, will be randomized to receive sitagliptin or placebo (see, 3.2.a). Due to the study design (i.e. need of surgical care), there will be no run-in period. Women in childbearing potential will have urine  $\beta$ -HCG measured to rule out pregnancy before participating in the study.

#### 3.2.a. Treatment Groups:



#### 3.2.b. Intervention:

A total of 220 patients with T2D will be consented and randomized prior to surgery. For patients consented in the outpatient setting their antidiabetic treatment will be modified as follows:

- **Oral treatment:** Insulin secretagogues (sulfonylureas and glinides), DPP-4 inhibitors will be discontinued 24 hours prior to surgery. *SGLT-2 inhibitors* will be discontinued 48 hours prior to surgery. All other oral antidiabetic agents will be continued until the day prior to surgery.
- **GLP-1 receptor agonists:** short-acting (liraglutide, exenatide) will be held 48 hours prior to surgery. Long-acting (exenatide ER, albiglutide, dulaglutide) will be held at least one week before surgery.
- **Insulin:** Pre-prandial insulin will be continued until the day prior to surgery. Basal (glargine, detemir, degludec) and NPH insulin dose is recommended to be decreased by 20%, the day prior to surgery.



Patients will receive sitagliptin or placebo starting the day before surgery and continue daily during the hospital stay. The day of surgery, antidiabetic therapy will be held and subjects will receive study drug. The dose of study drug will depend on the patient's GFR at time of randomization. Patients with a calculated GFR  $\geq 45$  mL/min/1.73m<sup>2</sup> will receive study drug 100mg daily. Patients with calculated GFR between 30-44 mL/min/1.73m<sup>2</sup> will receive study drug 50mg daily. If the calculated GFR drops below 30 mL/min/1.73m<sup>2</sup>, patients will receive study drug 25mg daily. If the calculated GFR changes after randomization, the study drug will be adjusted accordingly.

Recommendations to manage hospitalized patients prior to surgery:

- **Starting total daily insulin dose:**
- Insulin naïve patients (oral agents or no therapy)
  - Patients with BG between 140-200 mg/dL = 0.3 units per kg weight per day.
  - Patients with BG between 201-400 mg/dL = 0.4 units per kg weight per day.
  - The starting insulin TDD will be reduced to 0.25 units per kg in patients  $\geq 70$  years of age and/or with a GFR < 50 ml/min.
- Subjects treated with insulin prior to admission will receive 80% of the outpatient dose (basal or basal plus prandial) insulin dose.
  - Half of total daily dose will be given as basal (glargine or Levemir) and half as rapid-acting insulin analogs
  - Basal (Glargine/Levemir) insulin will be given once daily, at the same time of the day.
  - Rapid-acting insulin (lispro, aspart or glulisine) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose will be held.
- **Insulin adjustment.** The total daily BASAL insulin dose will be adjusted as follows:
  - Fasting and pre-meal BG between 100-140 mg/dl without hypoglycemia the previous day: no change
  - Fasting and pre-meal BG between 141-180 mg/dl: increase glargine dose by 10% every day
  - Fasting and pre-meal BG >180 mg/dl: increase glargine dose by 20% every day
  - Fasting and pre-meal BG between 70-99 mg/dl: decrease glargine dose by 10% every day
  - If a patient develops hypoglycemia (BG <70 mg/dL), decrease glargine dose by 20%.
  - If a patient develops hypoglycemia (BG <40 mg/dL), decrease glargine dose by 30-40%.
- **Supplemental insulin.** Supplemental (lispro, aspart or glulisine) insulin will be administered following the "sliding scale" protocol by Primary Care Team.
  - If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal and at bedtime 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 (6-12-6-12) following the "sensitive" dose of the sliding scale chosen by the Primary Care Team or healthcare facility.

If determined by the investigator or co-investigator that patient is insulin resistant, it would be to his/her medical discretion to adjust doses of basal and rapid acting insulin based on patient's needs.

**3.2.b.1 ICU Stay:** The study drug will be given once daily in a blinded fashion during the ICU and hospital stay. Study patients with hyperglycemia in the ICU (defined as a BG >180 mg/dL) will continue to receive the study drug (sitagliptin or placebo) and will be started on intravenous CII in the ICU adjusted to achieve and maintain a BG target between 110 - 180 mg/dl in the ICU.

Patients with hyperglycemia who require CII in the ICU will be started on the institution's insulin infusion protocol in the ICU. Below is the Emory insulin drip protocol:



(Target BG =110 – 180 mg/dL)

If bolus is ordered by MD, give 0.1 unit/Kg (IVP). Calculate initial IV Insulin infusion rate as follows

BG/ 100 = units/hour = mL/hour (round to nearest 0.1 Unit)

Check BG in 1 hour, titrate per protocol below. (Insulin drip= 1 unit/mL)

Did the BG increase or change by 30 mg/dL from the prior BG?

BG (mg/dL)	<u>WITH ANY INCREASE</u> in BG from prior BG	<u>BG DECREASE LESS than 30 mg/dL</u> from prior BG	<u>BG DECREASE GREATER than or EQUAL to 30 mg/dL</u> from prior BG
<b>241 or greater</b>	Increase rate by 3 units/hr	Increase rate by 3 units/hr	NO CHANGE
<b>211 – 240</b>	Increase rate by 2 units/hr	Increase rate by 2 units/hr	NO CHANGE
<b>181 – 210</b>	Increase rate by 1 unit/hr	Increase rate by 1 unit/hr	NO CHANGE
<b>141 – 180</b>	NO CHANGE	NO CHANGE	NO CHANGE
<b>110 – 140</b>	NO CHANGE	NO CHANGE	Decrease rate by 1/2
<b>91 – 109</b>	Decrease rate by 1/2	Decrease rate by 1/2	1. <b>HOLD</b> insulin drip. 2.Check BG q 1 hour: <b>Restart</b> infusion rate at 1/2 prior infusion rate <b>when BG greater than 180 mg/dL</b>

<b>71 – 90</b>	1. <b>HOLD</b> insulin drip. 2. Check BG q 30 min until BG is greater than 90mg/dL then check BG q 1 hr. 3. <b>Restart</b> prior infusion rate at 1/2 rate <b>when BG greater than 180 mg/dL</b>
<b>70 or Less</b>	1. <b>HOLD</b> insulin drip 2. Give IV D50 • BG 41 – 70 mg/dL: give 1/2 amp D50 IV or 8 ounce juice PO • BG 40 mg/dL or less: give 1 amp D50 IV 3. Repeat BG q 15 minutes until BG <b>greater than 70 mg/dL</b> , then check BG q 30 minutes until BG <b>greater than 90 mg/dL</b> 4. <b>BG greater than 90 mg/dL</b> ., Check BG q 1 hour; <b>Restart</b> infusion at 1/2 prior infusion rate <b>when BG greater than 180 mg/dL</b>

When BG reaches target (BG=110-180 mg/dL) for 2 consecutive readings, check BG q 2 hours

**Critical Values:** Treat for BG less than 45 mg/dL or greater than 450 mg/dL per protocol then Notify MD.

If patient's BG levels continue to increase after 2 interventions, notify MD.

### 3.2.b.2. Transition from Insulin Drip to Subcutaneous Insulin

The study drug will be given once daily in a blinded fashion until completion of 10 days of study treatment.

- Patients who didn't require CII or a rate <1 U/h:
  - Insulin naïve patients:
    - BG <180 mg/dL: Transition to SSI
    - BG >180 mg/dL: Start basal weight based at 0.2 U/kg plus SSI.
  - Patients with prior insulin treatment:
    - Start basal at pre-surgery dose plus SSI, or
    - Start basal weight based at 0.2 U/kg plus SSI.

- Patients that required continuous insulin infusion (CII) at a rate  $\geq 1$ U/h will be transitioned to basal insulin (glargine/detemir). Calculate total daily dose (TDD) of insulin from the average CII rate during the last four hours of infusion (example, if the average rate is 2 U/hr., the TDD is 48 U/day)
  - Give 50% of calculated dose as basal (glargine/detemir) insulin every day. Basal insulin will be given approx. 4 hours before discontinuation of CII.
  - Monitor BG AC and HS, if BG > 180 mg/dl x 2, start prandial (lispro / aspart) insulin at same basal dose divided in 3 equal doses before meals and coverage with sliding scale insulin for BG >180 mg/dl, see table 3.2.c.1.
- After transition to regular floor, patients not transitioned to basal insulin will continue to receive sitagliptin or placebo along with a supplemental sliding scale outlined in Table 3.2.c.1. During this period, if patients have 2 consecutive fasting and/or premeal BG >180 mg/dl, or with average daily BG >180 mg/dl, 180 mg/dL), rescue therapy will be initiated. **Rescue therapy with subcutaneous insulin (see 3.2.c.2)**

**Supplemental (correction) insulin.** Supplemental (lispro or aspart) insulin will be administered following the “sliding scale” protocol (Table 3.2.c.1.).

Table 3.2.c.1., Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose before meals.

Blood Glucose (mg/dL)	<input type="checkbox"/> Sensitive	<input type="checkbox"/> Usual	<input type="checkbox"/> 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

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\*\* Check appropriate column below and cross out other columns

At bedtime, give Sliding Scale Insulin starting at BG >240 mg/dl.

Blood Glucose (mg/dL)	<input type="checkbox"/> Sensitive	<input type="checkbox"/> Usual	<input type="checkbox"/> Resistant
241-280	1	2	3
281-320	2	3	4
321-360	3	4	5
361-400	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 = insulin dose at BG > 240 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.

### 3.2.c.2 Inpatient Rescue Therapy with Basal Bolus Insulin regimen:

Patients with persistent hyperglycemia (fasting and premeal BG > 180 mg/dl) while receiving basal plus correction regimen will be changed to basal bolus insulin regimen, calculated to give 50% of basal (glargine or detemir) insulin once daily and 50% of premeal rapid-acting insulin (lispro or aspart) before meals.

#### Basal Bolus Regimen: Starting total daily insulin dose:

- Starting total daily insulin dose (TDD) = 0.4 units per kg weight per day.
- Half of total daily dose will be given as basal and half as rapid-acting insulin analogs
- Basal insulin will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (even if NPO).
- Rapid-acting insulin (lispro, aspart) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of lispro will be held.

**Insulin adjustment.** The total daily insulin dose will be adjusted as follow:

- Fasting and/or pre-meal BG between 100-180 mg/dl without hypoglycemia the previous day: no change
- Fasting and/or pre-meal BG between >180-240 mg/dl: increase basal dose by 10% every day
- Fasting and/or pre-meal BG >241 mg/dl: increase basal dose by 20% every day
- Fasting and/or pre-meal BG <100 mg/dl: Decrease basal by 10%
- If a patient develops hypoglycemia (BG <70 mg/dL), the insulin TDD (basal and prandial) should be decreased by 20%.

**Supplemental (correction) insulin.** Supplemental (lispro or aspart) insulin will be administered following the “sliding scale” protocol (Table 3.2.c.1.).

**Blood glucose monitoring in non-ICU.** Blood glucose will be measured before each meal and at bedtime (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.

If determined by the investigator or co-investigator that patient is insulin resistant, it would be to his/her medical discretion to adjust doses of basal and rapid acting insulin based on patient’s needs.

### 3.2.b.3. Treatment recommendations at discharge:

- **Admission A1C < 7.5%:**
  - Discharge on same pharmacologic regimen (oral agents, insulin therapy).
  - Assure there are no contraindications to OAD (i.e., TZDs and heart failure; metformin and renal failure).
  - If contraindication to OADs, discharge patient on sitagliptin once daily.
- **Admission A1C between 7.5% and 9%:**
  - **Patients receiving OAD treatment prior to admission:**
    - If no contraindications to OAD discharge on metformin in combination to sitagliptin.
    - If contraindication to metformin, discharge on sitagliptin in combination to basal at 50% of total daily hospital dose.
    - If contraindication to metformin in a patient who did not receive basal in the hospital, discharge on sitagliptin once daily and basal at 0.15 unit/kg/day.
  - **Patients receiving OAD and insulin combination prior to admission:**
    - If no contraindications to OAD discharge on metformin in combination to sitagliptin.
    - If contraindication to metformin, discharge on sitagliptin in combination to basal at 50% of daily hospital dose.

- If contraindication to metformin in a patient who did not receive basal insulin in the hospital, discharge on sitagliptin once daily and basal insulin at 0.15 unit/kg/day.
- **Patients receiving insulin treatment prior to admission:**
  - Discharge on sitagliptin in combination with basal insulin at 50% of total daily hospital dose.
- **Admission A1C  $\geq$  9%:**
  - **Patients receiving OAD treatment prior to admission:**
    - If no contraindications to OAD discharge on metformin plus sitagliptin in combination to basal once daily at 80% of daily hospital.
    - If contraindication to metformin, discharge on sitagliptin in combination to basal at 80% of daily hospital dose.
    - If contraindication to metformin in a patient who did not receive basal in the hospital, discharge on sitagliptin once daily and basal at 0.15 unit/kg/day.
  - **Patients receiving OAD and insulin combination prior to admission:**
    - If no contraindications to OAD discharge on metformin plus sitagliptin in combination to basal insulin once daily at 80% of total daily hospital.
    - If contraindication to metformin, discharge on sitagliptin in combination with basal insulin at 80% of total daily hospital dose.
    - If contraindication to metformin in a patient who did not receive basal insulin in the hospital, discharge on sitagliptin once daily and basal insulin at 0.15 unit/kg/day.
  - **Patients receiving insulin treatment prior to admission:**
    - If no contraindications to OAD discharge on metformin plus sitagliptin in combination to basal insulin once daily at 80% of total daily hospital.
    - If contraindication to metformin, discharge on sitagliptin in combination to basal insulin at 80% of total daily hospital dose.
    - If contraindication to metformin in a patient who did not receive basal in the hospital, discharge on sitagliptin once daily and basal insulin at 0.15 unit/kg/day
    - **Alternative:** Discharge on basal bolus regimen at same inpatient total daily insulin dose.
      - Basal insulin (glargine or detemir) once daily, at the same time of the day.
      - Rapid-acting insulin (lispro, aspart, glulisine) before meals.

### 3.3. Primary and Secondary Research Outcomes:

#### Primary Outcome:

**3.3. a Aim 1:** To determine differences in the frequency of stress hyperglycemia (% patients with BG >180 mg/dl) in the ICU after CABG surgery between patients treated with sitagliptin or placebo.

**3.3. b. Aim 2:** To determine differences between groups on the number of patients with persistent hyperglycemia (2 consecutive fasting and/or premeal BG > 180 mg/dl, or with average daily BG >180 mg/dl) who require rescue therapy with SC insulin after discontinuation of CII.

**Secondary outcome** is to compare differences between treatment with sitagliptin and placebo on:



1. Need for CII for treatment of hyperglycemia
2. Mean ICU BG concentration
3. Mean insulin dose during ICU (insulin infusion per hour (unit/hour) and per day)
4. Duration of CII (hours on CII)
5. Number of patients requiring SC insulin after discontinuation of CII (transition ICU to floor)
6. Days of SC insulin after discontinuation of CII
7. Mean non-ICU BG concentration
8. Amount of SC insulin in ICU and non-ICU stay
9. Hyperglycemic events (BG  $\geq$  200 mg/dL) in ICU and non-ICU
10. Hypoglycemic events (BG < 70 mg/dl; severe hypoglycemia (BG < 40 mg/dl) in ICU and non-ICU.
11. Composite of perioperative complications including: hospital mortality, sternal wound infection (deep and superficial), bacteremia, pneumonia, acute renal failure, and acute myocardial infarction.
  - a. Surgical wound infection (superficial and deep sternal wound infection)
  - b. Pneumonia (CDC criteria)
  - c. Acute renal injury (new-onset increment serum creatinine level > 50% from baseline)
  - d. Acute myocardial infarction (AMI): (1) typical increase and gradual decrease (troponin) or (2) more rapid increase and decrease (creatine kinase MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms, (b) development of pathologic Q waves on the electrocardiogram, (c) electrocardiographic changes indicative of ischemia (ST-segment elevation or depression), or (d) coronary artery intervention (e.g., coronary angioplasty) <sup>77</sup>.
12. Duration of ventilatory support.
13. ICU and hospital length of stay, and ICU readmissions
14. Cerebrovascular events (permanent stroke and reversible ischemic neurologic deficit).
15. Hospital readmission and need for Emergency room visit after discharge (a short visit will be conducted at the time of their post-op visit or via telephone).

#### 4. CLINICAL MANAGEMENT GUIDELINES

The primary care team will provide care concerning the use of pressors, ventilatory support/weaning, sedation, antibiotics, and treatment of co-morbid conditions.

**4.1. Assessment and monitoring of BG concentration.** Information on BG measurements both at bedside by glucose meter and by hospital laboratory will be collected. BG will be measured every 1-2 hour during CII in the ICU, and before meals and at bedtime after transition to regular wards. Hypoglycemia is the main adverse event and safety issue in the study. The number of mild (BG  $\leq$  70 mg/dL) and severe hypoglycemia (BG  $\leq$  40 mg/dL) and clinical consequences (neurological and cardiovascular) will be compared between groups.

**4.2. Assessment and monitoring of hospital mortality.** Investigators daily will follow study subjects and date and presumed cause of death will be recorded. Information on the attending physician's summary of events surrounding subject's demise will also be documented.

**4.3. Assessment and monitoring of wound infections.** The investigators will review each subject's records daily from Monday to Friday regarding potential new infections. Data from the weekends will be collected the following Monday. Deep Sternal Wound Infection (DSWI): chest wound infection involving the sternum or mediastinal tissues, including mediastinitis; and Superficial Sternal Wound Infection (not involving the sternal bone or wires): chest wound infections involving the skin or subcutaneous tissues, or both.

**4.4. Assessment and monitoring of nosocomial infections.** The following daily information will be collected for nosocomial infection surveillance: 1) temperature curve, 2) white blood cell counts, 3) daily progress notes, 4) daily clinical microbiology laboratory data, 4) all relevant radiographic reports, 5) orders for antimicrobial agents, 6) communication, as needed, with primary physicians and site infectious disease consultants, 7) use of the CDC guidelines for diagnosis of specific nosocomial infections.<sup>78</sup>

- 4.5. Assessment and monitoring of days on mechanical ventilation.** The need for mechanical ventilation will be monitored daily. The day the subject is weaned from the ventilator will be recorded as a ventilator day.
- 4.6. Assessment and monitoring of length of SICU and hospital stay.** The morning location of the study subject (in either the SICU or surgical ward) and date of hospital discharge will be recorded daily.
- 4.7. Assessment and monitoring of renal function.** Acute kidney injury is defined as an increment level > 50% from baseline.
- 4.8. Cerebrovascular accident (CVA).** Defined as central neurologic deficit persisting more than 72 hours (permanent stroke), transient ischemic attack, deficit resolving within 24 hours, or deficit lasting more than 24 hours but less than 72 hours (reversible ischemic neurologic deficit).
- 4.9. APACHE II Scoring.** APACHE score will be calculated on arrival to ICU. The APACHE II score will be entered into the initial screening form following completion of CABG.
- 4.10. 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, and APACHE score. Daily information will be collected on treatment (insulin IV or SC and dosage, antibiotics, use of corticosteroids), nutrition support, BG and laboratory values, hospital complications and adverse events, and length of ICU and hospital stay. All data will be entered electronically in Redcap by participating sites. Sponsor site expects data to be entered in Redcap within 10 days of discharge, phone call or outpatient visit.

## **5. HUMAN SUBJECTS**

### **5.1. Study population.**

#### **5.1. a. Inclusion criteria:**

1. Males or females between the ages of 18 and 80 years undergoing any CABG surgery.
2. Patients with T2D treated with diet, oral, injectable agents, and/or insulin.

#### **5.1. b. Exclusion criteria:**

1. Patients with Type 1 Diabetes
2. Patients with history of diabetic ketoacidosis and/or hyperosmolar, hyperglycemia syndrome.
3. Severely impaired renal function (GFR < 30 ml/min) or clinically significant hepatic failure.
4. Moribund patients and those at imminent risk of death (brain death or cardiac standstill).
5. Subjects with gastrointestinal obstruction or adynamic ileus or those expected to require gastrointestinal suction.
6. Patients with clinically relevant pancreatic or gallbladder disease.
7. Treatment with oral or injectable corticosteroid.
8. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study,
9. Female subjects are pregnant or breast-feeding at time of enrollment into the study.

**5.2. Inform consent and randomization.** All patients scheduled to undergo cardiac surgery will be considered potential candidates in this study. Patients will be consented during the preoperative evaluation 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.

**5.3. Study Sites.** This study will be conducted at Emory University Hospitals and Grady Memorial

## 6. STATISTICAL ANALYSIS

The proposal is a two-arm, three-center, randomized placebo-controlled clinical trial. The primary hypothesis is that treatment with sitagliptin will prove to be a safe and effective for the prevention and treatment of hyperglycemia during the perioperative period cardiac surgery patients.

**6. a. Analysis of Primary Endpoint:** The primary endpoints in this study are to determine differences between sitagliptin and placebo treatment on: 1) frequency of hyperglycemia in the ICU after cardiac surgery, and 2) number of patients with persistent hyperglycemia who require rescue therapy with SC insulin after discontinuation of CII. We will first use two-sided Chi-square test or Fisher's exact test to compare the primary endpoint between the treatment group and the control group. 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. 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 also apply standard model selection and diagnostic procedures to determine and assess the final multivariate linear model.

**6. b. Analysis of Secondary Endpoints:** The secondary outcomes of interest can be a binary outcome (e.g. indicator for whether CII is needed in ICU), or a count outcome (e.g. number of perioperative complications), or a continuous outcome (e.g. mean daily BG concentration). We will adopt the same strategy proposed for the primary endpoint to analyze any binary or continuous secondary outcomes. For secondary endpoints measured as counts, we plan to use nonparametric tests such as Kruskal-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. 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.

**6. c. Sample Size Calculation and Power Analysis:** We have performed sample size and power calculations based on our prior studies. In the GLUCO-CABG trial, 91% of DM subjects had stress hyperglycemia in ICU. In this study, we assume the same rate of hyperglycemia in the control (placebo) group. We anticipate that sitagliptin will reduce the rate of hyperglycemia by 20-25% (corresponding to odds ratio (OR) in the range of 0.264-0.213). We calculate the sample size based on the OR estimate of 0.264 and provide the power for the larger treatment effects represented by OR=0.25, 0.20, and 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=0.264 (i.e. 91% vs 73%) would be 77 patients per study group. Accounting for 15-20% attrition rate, recruiting ~95 patients we need to be recruited in each group. A total of 200 randomized patients (100 patients per group) will be recruited in this study.

We also consider the statistical power for the primary endpoint for Aim 2 and important secondary endpoints. Based on the GLUCO-CABG trial, 98% of T2D subjects required SQ insulin post-transition. We assume the same rate for the placebo group in the proposed study, and expect 20-25% reduction in the rate of requiring SC insulin post-transition, which corresponds to OR in the range of 0.074-0.057. Given 77 patients per group (after attrition), we would have 97.8% power when the OR in this endpoint is 0.074. . We also calculate the power for

OR=0.07, 0.06, and 0.05 (Table). In the GLUCO-CABG data, the standard deviation (SD) of mean daily BG for T2D subjects is bounded above by 36 mg/dl. Assuming the same upper bound for the BG SD in this study, given 77 patients per group (after attrition), we would have over 80% power to detect a mean daily BG difference of 16.6 mg/dl between the two study groups, based on a two-sample, two-sided t-test, with  $\alpha=0.05$ . Our calculations suggest that the proposed study is well powered for the primary endpoint as well as the secondary endpoints of major interests.

Table. Power computed based on two-sided Fisher's exact test with  $\alpha=0.05$  and the proposed sample, 56 patients per group after attrition.

<b>Effect Size:</b>	0.264	0.25	0.20	0.15
Odds ratio				
<b>Primary endpoint: Stress hyperglycemia in ICU (placebo 96% event rate)</b>				
Event rates	91% vs. 73%	91% vs. 72%	91% vs. 67%	91% vs. 60%
Power	80.3%	84.3%	95.3%	>99%
<b>Secondary endpoint: Need for SC insulin post-transition (placebo 98% event rate)</b>				
<b>Effect Size:</b>	0.074	0.07	0.06	0.05
Odds ratio				
Event rates	98% vs. 78%	98% vs. 77%	98% vs. 75%	98% vs. 71%
Power	97.8%	98.5%	>99%	>99%

## 7. Data and Safety Monitoring Board (DSMB):

The Data and Safety Monitoring Board (DSMB) will review unblended data on safety, treatment compliance, and evaluate the efficacy of the intervention being studied in this clinical trial. The DSMB will meet at 6-month intervals and report on study progress to the IRB.

**8. 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 the rate of death and hospital complications (two-sided  $\alpha$  level,  $<0.01$ ) between the treatment groups.

## 9. ADVERSE EVENTS

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

## 9.1. Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

### **NOTE:**

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

## 9.2. Serious Adverse Event Collection and Reporting

The collection of AEs will start after the signing of the informed consent. All SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on an SAE Report Form or similar form (e.g. CIOMS, MedWatch); If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.



### 9.3. Nonserious Adverse Events

A **nonserious adverse event** is an AE not classified as serious.

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

### 9.4. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

## 9. Risk associated with participation:

**9.1. Hypoglycemia.** Hypoglycemia is the main adverse event and safety issue in the study. In our previous ICU studies, we observed that <10% of cardiac surgery subjects during CII and 20-30% during SC insulin experienced hypoglycemia. The use of insulin in combination with DPP4 inhibitors may increase the risk of hypoglycemia during the hospital stay. The number of mild ( $BG \leq 70$  mg/dL) and severe hypoglycemia ( $BG \leq 40$  mg/dL) and clinical consequences (neurological and cardiovascular) will be compared across treatment arms.

**9.2. Treatment of hypoglycemia.** Hypoglycemia, defined as a  $BG < 70$  mg/dL will be treated by a standard hypoglycemia protocol available at each hospital. In brief, insulin infusion will be turned off in the ICU or total daily dose of SC insulin will be reduced by 20-40% in non-ICU settings. In the ICU, subjects will receive Dextrose 50% solution (D<sub>50</sub>W) IV push based on the formula  $cc \text{ of } D_{50}W \text{ IV push} = (100 - BG) \times 0.4$ , or alternative D<sub>50</sub>W IV push dose: patient awake: 25 ml (1/2 amp), patient not awake (i.e. sedated): 50ml (1 amp). Blood glucose will be rechecked every 20 minutes and repeat 25ml of D<sub>50</sub>W IV if  $< 60$  mg/dL. Insulin infusion will be restarted once blood glucose is  $> 140$  mg/dL. In non-ICU patients will be treated with oral glucose if alert or with IV Dextrose (as above) if comatose.

**9.3. Hyperglycemia.** It is possible that following the proposed protocol, patients randomized to the conventional treatment arm will develop higher numbers of hyperglycemic events ( $BG > 200$  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.

**9.4. 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) patients will be closely monitored in the ICU, d) no patients with history of significant pancreatic, renal or hepatic failure will be recruited in this study, e) study subjects will receive rescue therapy with insulin in the event of hyperglycemia.

**10. 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.

**11. 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.

**12. 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.

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

**14. 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.

**15. Payment for participation.** Participation in this study is voluntary. Patients will receive one hundred dollars (\$100.00) prior to discharge. If a participant should stop participation before completion, the payment will be prorated at \$20.00 per day.

**16. Financial conflict of interests.** This study receives support from Merck. Dr. Umpierrez, Dr. Pasquel, and Dr. Vellanki serve as a consultant to Merck and receives compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

**17. Study time line:** More than 1200 major cardiac surgeries are performed every year at Emory University Hospital, Midtown Hospital and Grady Memorial Hospital. We anticipate that >80% of patients without a history of DM will experience stress hyperglycemia (BG>140 mg/dl) after surgery, giving 4 to 6 potential candidates per week. Historically we averaged 8–12 subjects/week requiring insulin infusion at the 3 institutions. We anticipate recruiting 2 or 3 patients per week (one per institution) for a total recruitment period of approximately 12 months.

## **18. RESPONSIBILITIES OF THE SPONSOR**

Emory University will serve as Sponsor of this Clinical Trial. The sponsor is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded. As the Monitoring Team, we will help the Investigators in maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, a member of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems will contact all research sites, through letters or telephone calls. These monitoring contacts will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, patient compliance, concomitant therapy use and quality of data.

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