Table 1. AEs of Special Interest

AE	Incidence and Outcome
Pancreatitis	1 withdrawal, 1 recovered and continued
Pancreatic carcinoma	1 withdrawal
Acute renal failure	4 patients
MACE (serious MI or stroke AEs)	9 patients (3.1%)
MACE (serious MI, unstable angina, stroke, transient ischemic attack, or heart failure AEs)	13 patients (4.4%)

AE, adverse event; MACE, major adverse coronary event; MI, myocardial infarction.

occurrences of major hypoglycemia, observed with long-term treatment. The most common adverse events (AEs) reported included upper respiratory tract infection (43%), nasopharyngitis (29%), diarrhea (27%), sinusitis (24%), and arthralgia (21%). Nausea (mostly mild) and injection-site reactions were the most common AEs with exenatide once weekly during the first 30 weeks, but these were not the most common AEs in the 6 years of follow-up.

Treatment-emergent AEs leading to withdrawal from week 30 to 6 years were infrequent (6.6%); 107 serious AEs were reported in 61 patients from week 30 to year 6. AEs of special interest are listed in Table 1.

In conclusion, long-term therapy with once-weekly exenatide is feasible and well tolerated. This treatment regimen resulted in sustained improvements in glycemic control and weight over 6 years in the 40% of enrollees who continued therapy.

GLUCO-CABG: No Reduction in Perioperative Complications to Cardiac Surgery With Intensive Control of Hyperglycemia

Written by Dennis Bittner

Hyperglycemia is a common condition among cardiac surgery patients, and it occurs in approximately half of all patients following surgery. Although it is agreed that controlling hyperglycemia reduces risk of organ failure, infection, and mortality, the ideal target range for blood glucose (BG) in the perioperative period remains unknown. The 2009 American Diabetes Association (ADA) guidelines recommended a range of 140 to 180 mg/dL BG in intensive care unit (ICU) patients [Moghissi ES et al. *Endocr Pract.* 2009], but the intensive glucose control required to deliver this range results in severe hypoglycemia (<40 mg/dL) in 5% to 20% of ICU patients [Umpierrez et al. *J Clin Endocrinol Metabol*. 2002].

Guillermo Umpierrez, MD, Emory University School of Medicine, Atlanta, Georgia, USA, presented results from the GLUCO-CABG trial [NCT01792830]. The objective of this randomized, controlled study was to determine if intensive glucose control while the patient is in the ICU following coronary artery bypass grafting (CABG) can improve outcomes. The primary end point was a composite end point that included a variety of potential surgical complications. The study included men and women between 18 and 80 years, with or without a history of diabetes, who had undergone CABG with or without valve surgery, and had displayed hyperglycemia (defined as BG>140 mg/dL) either during surgery or during their stay in the ICU. At baseline, patient characteristics were similar between the 2 treatment groups (Table 1).

Patients were randomized to either intensive control of BG (range, 100 to 140 mg/dL) using computer algorithm to guide the infusion of insulin or conservative therapy within the ADA-recommended range (141 to 180 mg/dL). After attrition, a total of 148 patients in each group achieved 80% power for the study to detect an odds ratio of 0.35 in composite outcome ($\alpha = 0.05$).

In the 90 days following hospital discharge, patients treated with intensive glucose control in the ICU had a 42% rate of surgical complications, compared with 52% in patients treated with conservative control (Figure 1). The difference between the 2 groups was not significant, however, on a composite of complications that included death, pneumonia, acute kidney injury (AKI), respiratory

Table 1. Patient Characteristics at Baseline

	Intensive	Conservative	*P* Value
Number of patients	151	151	—
Female/male, n	45/106	39/112	.44
Race, W/B/O	110/35/6	111/34/6	1.00
Age, y	64 ± 9	64 ± 10	.84
BMI, kg/m^2	31 ± 7	30 ± 7	.40
History of DM, n (%)	77 (51)	75 (50)	.82
Duration of DM, y	11 ± 9	11 ± 10	.72
APACHE score	22 ± 3	22 ± 4	.12
BG admission, mg/dL (mmol/L)	140 ± 60 (7.8 ± 3.3)	143 ± 65 (7.9 ± 3.6)	.44

APACHE, Acute Physiology and Chronic Health Evaluation; BG, blood glucose; BMI, body mass index; DM, diabetes mellitus; W/B/O, white/black/other.

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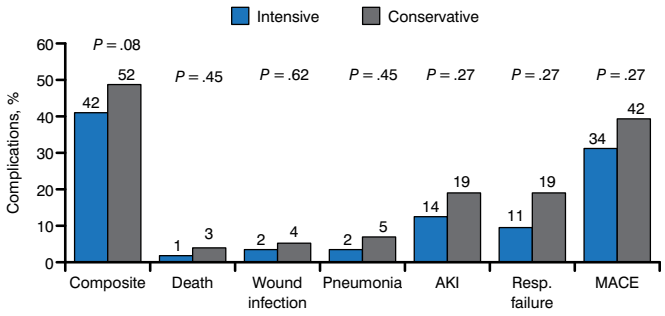
Figure 1. Comparison of Intensive and Conservative Glucose Control on Perioperative Complications



AKI, acute kidney injury; Resp., respiratory; MACE, major cardiovascular events.
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failure, wound infections, or major cardiovascular events (MACEs) (P=.08).

Composite of complications: death, wound infection, pneumonia, AKI, respiratory failure, and MACEs. Low rates of hypoglycemia were achieved using the computer algorithm to guide insulin infusion, and no patients had a BG < 40 mg/dL (2.2 mmol/L).

In summary, this study found that intensive glucose control in patients with hyperglycemia undergoing CABG surgery that targeted a BG of 100 to 140 mg/dL during the perioperative period did not significantly reduce complications or mortality compared with a less strict target of 141 to 180 mg/dL.

Effects of PDE-5 Inhibition in Patients With T2DM

Written by Maria Vinall

Tadalafil is a phosphodiesterase-5 (PDE-5) inhibitor used in the treatment of erectile dysfunction and pulmonary hypertension, and it was shown in a small study to increase forearm glucose uptake (FGU) and capillary recruitment in postmenopausal women with type 2 diabetes mellitus (T2DM) [Jansson PA et al. *Díabetologia*. 2010]. Lovisa Sjögren, MD, University of Gothenburg, Gothenburg, Sweden, presented results from the Effects of PDE-5 Inhibition on Postprandial Hyperglycemia in Type 2 Diabetes study [NCT01238224], which investigated the effect of tadalafil on postprandial hyperglycemia and circulating levels of proinflammatory markers in patients with T2DM after a mixed meal. The final results of this study indicate that tadalafil 20 mg may induce positive metabolic and vascular effects in the postprandial state in patients with T2DM.

Patients with obesity, insulin resistance, and T2DM have postprandial hyperglycemia and impaired postprandial microvascular response. Endothelial dysfunction, characterized by decreased production and release of nitric oxide (NO) into the vessels, and increased amounts of endothelin-1 (ET-1), a vasoconstricting proinflammatory peptide, are also common.

This was a randomized, double-blind, placebo-controlled, investigator-initiated trial that included 26 patients with T2DM (duration 3 months to 10 years) who were aged 40 to 70 years (men) or 50 to 70 years (women), with body mass indexes (BMIs) between 27 and 40 kg/m^2 and HbA_{1c} levels < 60 mmol/mol. After an overnight fast, patients were randomized to either tadalafil 20 mg (n = 14) or placebo (n = 12) 30 minutes prior to a mixed meal containing 47% fat, 7% protein, and 46% carbohydrates (786 kcal). All patients underwent continuous FGU, muscle microdialysis, and blood sampling for 5 hours. The objective of this study was to assess a treatment strategy in which NO signaling is amplified through PDE-5 inhibition.

Participants had a mean age of 61 years and a mean BMI of 30 kg/m^2, and the majority were men (17 of 26). Patients in the tadalafil group had significantly longer disease duration (60 months) compared with the placebo group (24 months) (P<.05). Circulating levels of glucose and insulin did not differ between the 2 groups before, during, or after the meal; there was also no difference for triglycerides or free fatty acids. The incremental areas under the curve (IAUC) for FGU, capillary recruitment, forearm blood flow (FBF), and ET-1 did not differ significantly, although there was a tendency toward an increased IAUC with the tadalafil group in the first 3 measures.

Because angiotensin-converting enzyme (ACE) inhibitors are known to have positive effects on glucose metabolism, the investigators conducted a post hoc analysis excluding patients taking this family of drugs, resulting in a subgroup of 20 patients who were not on ACE inhibitors (10 from the tadalafil group and 10 from the placebo group). Circulating glucose, triglyceride, free fatty acid levels, and insulin peak did not differ significantly between the 2 groups. Patients not on ACE inhibitors did, however, have a significant increase in the IAUCs for capillary recruitment, FGU, and FBF, and a decrease in ET-1 (P<.05).