The Society of Thoracic Surgeons Practice Guideline Series: Blood Glucose Management During Adult Cardiac Surgery

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The prevalence of diabetes mellitus in patients requiring cardiac surgery is rapidly increasing. These patients have higher perioperative morbidity and mortality, significantly reduced long-term survival, and less freedom from recurrent episodes of angina [1–3]. There is now evidence to suggest that achieving glycemic control in patients with diabetes decreases perioperative morbidity and improves short-term and long-term survival.

Despite the emerging recognition of the importance of glycemic control, there are no specific guidelines for cardiac surgeons as to what the optimal level of glucose should be during the perioperative period, and the best method to achieve these target values. What follows is an executive summary of guidelines for the management of hyperglycemia in both patients with and without diabetes undergoing adult cardiac surgical procedures, derived from evidence-based recommendations (Table 1).

I. Detrimental Effects of Hyperglycemia in the Perioperative Period

Key Points: Poor Perioperative Glycemic Control is Associated With Increased Morbidity and Mortality

Doenst and coworkers [4] retrospectively reviewed the effects of hyperglycemia on the clinical outcomes of 6,280 patients undergoing cardiac surgical procedures.

Higher glucose levels during surgery were found to be an independent predictor of mortality in patients with and without diabetes. Fish and coworkers [5] retrospectively reviewed the importance of blood glucose levels in the intraoperative and immediate postoperative period to predict morbidity in 200 consecutive coronary artery bypass graft (CABG) patients. A postoperative serum glucose level (> 250 mg/dL) was associated with a 10-fold increase in complications. Similar findings were reported by McAlister and coworkers [6] in a retrospective study of 291 patients undergoing CABG surgery. The average serum glucose level on the first postoperative day significantly predicted the development of an adverse outcome. The detrimental effects of elevated intraoperative glucose levels were also reported in a retrospective, observational study of 409 cardiac surgical patients by Gandhi and coworkers [7]. Intraoperative hyperglycemia was an independent risk factor for perioperative complications, including death. Abnormal glucose values prior to surgery may also be predictors of decreased survival after surgery. Lastly, Anderson and coworkers [8] studied the effect of elevated fasting blood glucose levels prior to surgery in a group of 1,375 CABG patients. Patients with elevated fasting blood glucose had a 1-year mortality that was twice as great as patients with normal fasting values and equal to that of patients who were suspected, or known to have diabetes mellitus.

Collectively, these studies strongly suggest that increased fasting glucose levels prior to surgery, and persistently elevated glucose levels during and immediately after cardiac surgery, are predictive of increased perioperative morbidity and mortality in patients with and without diabetes. The next section will review those studies showing that lowering perioperative glucose levels with insulin therapy will decrease morbidity and mortality in cardiac surgical patients.

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Table 1. Classification System Used for Evidence Based Recommendations

- Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
- Class IIA: Weight of evidence/opinion is in favor of usefulness/efficacy
- Class IIB: Usefulness/efficacy is less well-established by evidence/opinion.
- Class III: Conditions for which there is evidence or general agreement that the procedure/treatment is not useful/effective, or both, and in some cases may be harmful
- Level of Evidence—A: Data derived from multiple randomized clinical trials
- Level of Evidence—B: Data derived from a single randomized trial or nonrandomized studies
- Level of evidence—C: Only consensus opinion of experts, case studies, or standard-of-care

II. Beneficial Effects of Glycemic Control on Clinical Outcomes During Cardiac Surgery

Key Points: Glycemic Control (< 180 mg/dL) in Patients With Diabetes During Cardiac Surgery:

- Reduces mortality
- Reduces morbidity
- Lowers the incidence of wound infections
- Reduces hospital length of stay
- Enhances long-term survival

One of the earliest studies to examine the effects of glycemic control during cardiac surgery was reported by Furnary and coworkers [9]. The study involved 3,554 patients undergoing CABG surgery from 1987 to 2001. Patients were divided into three groups based on the year of surgery, the method of glycemic control, and the targeted glucose levels. From 1987 to 1991, patients received subcutaneous insulin, given every 4 hours to keep serum glucose < 200 mg/dL. From 1991 to 1998, a continuous intravenous (IV) insulin infusion was used to keep serum glucose between 150 and 200 mg/dL. From 1998 to 2001, the Portland protocol was instituted, which used a continuous insulin drip to keep serum glucose between 100 and 150 mg/dL. Continuous insulin infusions resulted in significantly lower mean glucose levels than could be obtained with intermittent subcutaneous insulin therapy. The perioperative mortality in CABG patients with diabetes was decreased by 50% after 1992 (4.5% vs 1.9%; $p < 0.0001$) when continuous insulin protocols were instituted, and it was similar to that for nondiabetic CABG patients. There was also a significant decrease in the incidence of deep sternal wound infections ($p < 0.001$). Furnary and coworkers [10] expanded their original series to include an additional 1,980 patients managed with the Portland protocol from 2001 to 2005. They introduced a new method to assess glycemic control called 3-blood glucose, or "3-BG," consisting of the average of all glucose values obtained on the day of surgery and the first and second postoperative days. An

increase in 3-BG was an independent predictor of perioperative mortality ($p < 0.001$). Mean 3-BG was also significantly related to the incidence of deep sternal wound infections, hospital length of stay, blood transfusions, new onset atrial fibrillation, and low cardiac output syndrome.

Further evidence to support the role of insulin therapy in the CABG patient with diabetes was presented by Lazar and coworkers [11] using a modified glucose-insulin–potassium solution. In this trial involving 141 patients with diabetes undergoing isolated CABG surgery, patients were prospectively randomized to receive glucose-insulin–potassium to keep serum glucose between 120 and 180 mg/dL, or sliding scale insulin coverage to maintain glucose < 250 mg/dL. The glucose-insulin–potassium was started on induction of anesthesia and continued for 12 hours in the intensive care unit (ICU). The glucose-insulin–potassium-treated patients achieved significantly better glycemic control immediately prior to cardiopulmonary bypass (169 mg/dL vs 209 mg/dL; $p < 0.0001$), and after 12 hours in the ICU (134 mg/dL vs 266 mg/dL; $p < 0.0001$). Patients treated with tight glycemic control had significantly higher cardiac indices ($p < 0.0001$) and less need for inotropic support ($p < 0.05$) and pacing ($p < 0.05$). Tighter glycemic control also resulted in a lower incidence of infections (0% vs 13%; $p = 0.01$) and atrial fibrillation (15% vs 60%; $p = 0.007$). This all contributed to a shorter hospital length of stay (6.5 days vs 9.2 days; $p = 0.0003$). After 5 years, the Kaplan-Meier curves showed a significant survival advantage ($p = 0.04$) for patients receiving better glycemic control. They had a significantly lower incidence of recurrent ischemia ($p = 0.01$) and wound infections ($p = 0.03$), and were able to maintain a lower angina class ($p = 0.03$).

The importance of tight glycemic control in patients undergoing CABG surgery was also demonstrated in a study by Van den Berghe and coworkers [12] involving 1,548 ventilated patients admitted to a surgical ICU. In this prospective, randomized study, 62% of patients had undergone cardiac surgery, and only 13% had a prior history of diabetes. During their ICU stay, patients were randomized to a conventional therapeutic group in which insulin was administered only if serum glucose exceeded 215 mg/dL to maintain a target goal of 180 to 200 mg/dL, and an intensive group that received a continuous insulin infusion to maintain glucose levels between 80 and 110 mg/dL. Intensive insulin therapy resulted in a significant reduction in mortality (10% vs 20%; $p = 0.005$), exclusively in those patients who required ≥ 5 days of ICU care with multiorgan failure and sepsis. Similarly, cardiac surgical mortality was only reduced in those patients requiring ≥ 3 days of ICU care. Hospital mortality for all cardiac surgical patients, irrespective of their ICU stay, was reduced from 5.1% to 2.1% ($p < 0.05$). Intensive glycemic control had no effect on morbidity and mortality in those patients spending ≤ 3 days in the ICU. In a further attempt to identify those patients who might benefit most from tight glycemic control, D'Alessandro and coworkers [13] sought to correlate the effect of tight

glycemic control with expected EuroScore outcomes in CABG patients with diabetes. Three hundred patients with diabetes undergoing CABG surgery from January 2003 to June 2004 receiving tight glycemic control (150 to 200 mg/dL in the operating room; ≤ 140 mg/dL in the ICU) were matched with 300 CABG patients with diabetes treated from March 2001 to September 2002, when insulin protocols were not present, using propensity-based analyses. The group with tight glycemic control had an observed mortality that was significantly lower than expected (1.3% vs 4.3%; $p = 0.01$). Mortality was especially lower in the higher risk cohort (EuroScore > 4; 2.5% vs 8.0%; $p = 0.03$). In contrast, there was no difference between observed and expected mortality in the group without tight glycemic control in patients with EuroScore < 4. Two additional studies have shown the importance of glycemic control in lowering sternal wound infections. Zerr and coworkers [14] studied the effects of glycemic control on the incidence of sternal wound infections in 1,585 CABG patients with diabetes. Sternal wound infections increased from 1.3% in patients with mean glucose values of 100 to 150 mg/dL to 6.7% in patients with levels of 250 to 300 mg/dL. In a retrospective study involving CABG patients with diabetes, Hruska and coworkers [15] found that a continuous insulin infusion maintaining glucose levels between 120 to 160 mg/dL significantly decreased the incidence of sternal wound infections compared with intermittent subcutaneous injections.

III. Glycemic Control in Patients Without Diabetes During Cardiac Surgery

Key Points: Intraoperative Glycemic Control Using Intravenous Insulin Infusions is Not Necessary in Cardiac Surgery Patients Without Diabetes Provided That Glucose Values Remain < 180 mg/dL

Is tight glycemic control necessary for all patients undergoing cardiac surgery? Butterworth and coworkers studied the effects of tight glycemic control in 381 patients without diabetes undergoing isolated CABG surgery [16]. In this prospective, randomized trial, one group received an insulin infusion when intraoperative glucose levels exceeded 100 mg/dL. The other group received no insulin coverage. The primary outcome was the incidence of new neurologic, neuro-ophthalmologic, or neurobehavioral deficits, or neurologic-related deaths. Intraoperative glucose levels were significantly lower in the patients who received an insulin infusion; however, there was no difference between the incidences of neurologic complications between the groups. Furthermore, there was no difference in operative mortality, need for inotropic support, or length of hospital stay between the groups, despite the fact that patients without intraoperative insulin had glucose levels ≥ 200 mg/dL. In this study, intraoperative glycemic control failed to improve short-term or long-term clinical outcomes in a group of patients without diabetes.

Gandhi and coworkers [17] looked at the effects of intensive intraoperative insulin therapy in 400 elective CABG patients. Patients were prospectively randomized to a continuous insulin group to maintain serum glucose between 80 and 100 mg/dL, or a conventional group targeted to keep serum glucose < 200 mg/dL using intermittent boluses of intravenous (IV) insulin. The incidence of diabetes was 20% in both groups. There was no difference in the primary outcome between the groups, which consisted of the composite incidence of death, sternal wound infections, prolonged ventilation, cardiac arrhythmias, strokes, and renal failure within 30 days of surgery. There was also no difference in ICU or hospital stay between the groups. There was a tendency for more deaths ($p = 0.06$) and strokes ($p = 0.02$) in the intensive insulin group. This study was limited in that it included patients both with and without diabetes, and both groups received intensive insulin therapy in the immediate postoperative period.

IV. Management of Hyperglycemia Using Insulin Protocols in the Perioperative Period Recommendations: Class I

- Glycemic control is best achieved with continuous insulin infusions rather than intermittent subcutaneous insulin injections or intermittent IV insulin boluses (level of evidence = A).
- All patients with diabetes undergoing cardiac surgical procedures should receive an insulin infusion in the operating room, and for at least 24 hours postoperatively to maintain serum glucose levels ≤ 180 mg/dL (level of evidence = B).

Intravenous insulin therapy is the preferred method of insulin delivery during the perioperative period. It allows for rapid titration, which facilitates glycemic control during periods of malabsorption, insulin deficiency, and resistance [18]. Table 2 describes various protocols that are readily available for use and target glucose values that can be achieved. Choosing an insulin infusion protocol is dependent on the needs and resources of the institution. To ensure safe and effective implementation of any protocol, those individuals involved in the patients' care must be comfortable using it. The success of any protocol can be determined by outcomes such as the time needed to achieve the target value, specific BG concentrations, average BG control, percentage of values in the desired range, or an area under-the-curve calculation reported as the percentage of time spent in a determined range [19]. This issue is addressed specifically on the American Association of Clinical Endocrinologists website for hospital management of hyperglycemia [20, 21]. For safety tracking, the number of episodes (or percent) of hypoglycemic events and any clinical consequences should be monitored.

Table 2. List of Published and Commercially Available Variable-Rate Insulin Infusion Protocols

Glucose Target Protocol	Brief Description	mg/dL	Reference
Markovitz	Five algorithms with pre-calculated rates using a multiplier; infusion rates are determined for each glucose range	120–199	27
Leuven	General guidelines on titration of insulin drip	80–110	12
Yale	Calculated rates based on glucose value and rate of change	90–120	20
Portland	Specified infusion rates by glucose range with IV bolus as needed; five target ranges are available for both ICU and floor	70–110 80–120 100–150 125–175 150–200	10
DIGAMI	Specified infusion rates by glucose range	126–180	28
University of Washington	Four algorithms with pre-calculated rates using a multiplier; infusion rates are determined for each glucose range	80–180	29
Atlanta Medical Center	10 algorithms with pre-calculated rates using a multiplier; infusion rates are determined for each glucose range	80–110	30
Glucommander	Computer calculated infusion rates based on programmed algorithms	80–120	31
Clarian	Computer calculated infusion rates based on glucostabilizer programmed algorithms	80–110	32

DIGAMI = diabetes and insulin-glucose infusion in acute myocardial infarction;   ICU = intensive care unit;   IV = intravenous.

V. Preoperative Management and Assessment for Patients With Diabetes Recommendations: Class I

- Patients taking insulin should hold their nutritional insulin (lispro, aspart, glulisine, or regular) after dinner the evening prior to surgery (level of evidence = B).
- Scheduled insulin therapy, using a combination of long-acting and short-acting subcutaneous insulin, or an insulin infusion protocol, should be initiated to achieve glycemic control for in-hospital patients awaiting surgery (level of evidence = C).
- All oral hypoglycemic agents and noninsulin diabetes medications should be held for 24 hours prior to surgery (level of evidence = C).
- The hemaglobin A1c (HbA$_{1c}$) level should be obtained prior to surgery in patients with diabetes or those patients at risk for postoperative hyperglycemia to characterize the level of preoperative glycemic control (level of evidence = C).

Class IIA

- Prior to surgery, it is reasonable to maintain blood glucose concentration ≤ 180 mg/dL (level of evidence = B).

Efforts should be made to optimize glucose control prior to surgery, because poor preoperative glycemic control has been associated with increased morbidity, including a higher incidence of deep sternal wound infections and prolonged postoperative length of stay [10, 11]. In general, all oral diabetes medications should be withheld within the 24 hours prior to surgery, especially sulfonylureas (eg, glipizide) and glinides (eg, nateglinide or repaglinide). These drugs can induce hypoglycemia in the absence of food. Patients who are taking insulin and who are admitted on the day of surgery should be instructed to continue their basal insulin dose (eg, glargine, detemir, or NPH) and hold their nutritional insulin (eg, lispro, aspart, glulisine, or regular) unless instructed otherwise by their primary physician. The NPH insulin may be reduced by one half or one third prior to surgery to avoid hypoglycemia.

To achieve rapid control in a hospitalized patient with hyperglycemia (glucose persistently > 180 mg/dL for > 12 hours before surgery), insulin therapy either with intravenous variable-rate continuous infusion or subcutaneous basal plus rapid-acting insulin should be used depending on the availability of either therapy. For the patient noted to be hyperglycemic in the preoperative area on the day of surgery, IV insulin therapy is an effective way to achieve rapid control. Patients with a known history of diabetes (either type 1 or type 2) can be started immediately on IV therapy in the preoperative area. All preoperative medications should be reviewed to determine the potential for insulin resistance. These include steroids, protease inhibitors, and anti-psychotic drugs. Finally, patients with renal insufficiency should be identified, because insulin clearance is impaired and the risk for hypoglycemia is increased.

The hemaglobin A1c (HbA$_{1c}$), a glycosylated hemoglobin, is an accurate indicator of glycemic control for a 2-month to 3-month period. The American Diabetes Association has reported that adequate glycemic control is associated with an HbA$_{1c}$ ≤ 7% [21]. Obtaining an HbA$_{1c}$ prior to surgery in diabetic patients or those patients at risk for postoperative hyperglycemia will help to optimize glycemic control in those patients with ele-

vated HbA1$_c$ levels. It will also identify those patients who might require more aggressive glycemic control upon hospital discharge.

VI. Intraoperative Control Recommendations: Class I

- Glucose levels > 180 mg/dL that occur in patients without diabetes only during cardiopulmonary bypass may be treated initially with a single or intermittent dose of IV insulin as long as levels remain ≤ 180 mg/dL. However, in those patients with persistently elevated serum glucose (> 180 mg/dL) after cardiopulmonary bypass, a continuous insulin drip should be instituted, and an endocrinology consult should be obtained (level of evidence = B).
- If an intravenous insulin infusion is initiated in the preoperative period, it should be continued throughout the intraoperative and early postoperative period according to institutional protocols to maintain serum glucose ≤ 180 mg/dL (level of evidence = C).

Patients receiving IV infusions of insulin should have their blood glucose monitored every 30 to 60 minutes. More frequent monitoring, as often as every 15 minutes, should be made during periods of rapidly fluctuating sensitivity, such as during the administration of cardioplegia and systemic cooling and rewarming. Patients with IV insulin infusions initiated in the preoperative period should have them continued in the operating room (OR) to maintain serum glucose < 180 mg/dL.

Patients with no history of diabetes prior to surgery, may exhibit transient elevation of BG > 180 mg/dL during cardiopulmonary bypass. These patients may have insulin resistance and should be treated with a single or intermittent dose of IV insulin to maintain glucose ≤ 180 mg/dL. Caution should be exercised in initiating a continuous IV insulin drip in these patients, because insulin requirements may decrease rapidly in the immediate postoperative period resulting in serious hypoglycemia [22]. However, those patients not known to have diabetes who have persistently elevated glucose values (> 180 mg/dL) during surgery should receive a continuous IV insulin drip. Because a large percentage of these patients may ultimately be found to have diabetes mellitus, an endocrinology consult should be obtained in the postoperative period.

VII. Glycemic Control in the ICU Recommendation: Class I

- Patients with and without diabetes with persistently elevated serum glucose (> 180 mg/dL) should receive IV insulin infusions to maintain serum glucose < 180 mg/dL for the duration of their ICU care (level of evidence = A).
- All patients who require ≥ 3 days in the ICU because of ventilatory dependency or requiring the

need for inotropes, intra-aortic balloon pump, or left ventricular assist device support, anti-arrhythmics, dialysis, or continuous veno-venous hemofiltration should have a continuous insulin infusion to keep blood glucose ≤ 150 mg/dL, regardless of diabetic status (level of evidence = B).
- Before intravenous insulin infusions are discontinued, patients should be transitioned to a subcutaneous insulin schedule using institutional protocols (level of evidence = B).

Patients with or without diabetes mellitus who have persistently elevated serum glucose > 180 mg/dL should receive intravenous insulin infusions to maintain serum glucose < 180 mg/dL [9–12]. Furthermore, those patients who require ≥ 3 days of ICU care due to prolonged ventilatory support, inotropic or mechanical support, renal insufficiency, or need for anti-arrhythmic therapy should have continuous IV insulin infusions to keep blood glucose < 150 mg/dL [10, 12]. When patients are receiving IV insulin infusions in the ICU, glucose levels should be monitored at least hourly until stable. This frequency avoids fluctuations in glucose levels and minimizes the risk of hypoglycemia, which is fortunately rare and has resulted in minimal morbidity [10–12].

When patients are ready to be discharged from the ICU, patients should be transitioned to a subcutaneous insulin-dosing schedule. Daily insulin requirements can be estimated by extrapolating the amount of insulin required in the preceding 24 hours and considering the patients' current nutritional intake [23].

VIII. Glycemic Control in the Stepdown Units and on the Floor Recommendations: Class I

- A target blood glucose level < 180 mg/dL should be achieved in the peak postprandial state (level of evidence = B).
- A target blood glucose level ≤ 110 mg/dL should be achieved in the fasting and pre-meal states after transfer to the floor (level of evidence = C).
- Oral hypoglycemic medications should be restarted in patients who have achieved target blood glucose levels if there are no contraindications. Insulin dosages should be reduced accordingly (level of evidence = C).
- According to the American Association of Clinical Endocrinologists, a reasonable goal for a noncritically ill patient on a regular hospital ward is < 110 mg/dL pre-meal and < 180 mg/dL postprandial or randomly [24]. The best method to achieve this control is with scheduled subcutaneous basal and, or bolus insulin therapy, such as glargine or determir (basal) and lispro, aspart, or glulisine (bolus). Patients with type 2 diabetes who have used oral diabetes medications preoperatively can be restarted on those medications once they have reached their targeted glucose goals and are eating a regular diet. Metformin should not be restarted until stable renal function has been docu-

mented. Thiazolidineadiones (eg, pioglitazone, rosiglitazone) can be re-started in patients without congestive heart failure or liver dysfunction.

IX. Preparation for Hospital Discharge Recommendations: Class I

- Prior to discharge, all patients with diabetes and those who have started a new glycemic control regimen, should receive in-patient education regarding glucose monitoring, medication administration (including subcutaneous insulin injection if necessary), nutrition, and lifestyle modification (level of evidence = C).
- Upon discharge, changes in therapy for glycemic control should be communicated to primary care physicians, and follow-up appointments should be arranged with an endocrinologist when appropriate (level of evidence = C).

All patients with hyperglycemia after cardiac surgery should be assessed by an inpatient diabetes team to decide on a glycemic control program after discharge. When hyperglycemia is discovered for the first time in the perioperative period, or if insulin is first being administered, or when a new insulin protocol is instituted, the patient should receive specialized education prior to discharge. This can be provided by a certified diabetes educator, and supplemented by nurses or registered dieticians with expertise in diabetes. Education should be started at least 2 days prior to discharge, including techniques of glucose monitoring, administration of medications, nutrition, exercise, and lifestyle modification [25, 26]. Appropriate follow-up should be arranged with primary care physicians prior to discharge. Referring physicians should be informed of any changes made in the diabetes management plan.

IX. Future Areas of Study

Important issues in the management of hyperglycemia during cardiac surgery remain to be elucidated. Future studies will determine: (1) the optimal level of glycemic control and which, if any, specific time in the perioperative period is most crucial for maintaining glycemic control; (2) whether the level of glucose achieved is as important as the amount of insulin delivered; and (3) the importance of preoperative HbA_{1c} levels and whether surgery should be delayed in patients with higher values. These studies will increase our understanding of hyperglycemia during cardiac surgery and help us to determine the most optimal methods to achieve glycemic control and improve clinical outcomes in these high-risk patients.

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