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Perioperative Management of Hyperglycemia and Diabetes in Cardiac Surgery Patients

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INTRODUCTION

The prevalence of diabetes mellitus is rising at an alarming rate, affecting 415 million people worldwide and approximately 30 million people in the United States in 2015.¹

Approximately half a million patients undergo coronary artery bypass graft surgery (CABG) each year in the United States.² Nearly 30% to 40% of patients undergoing cardiac surgery have a history of diabetes^{3,4} and approximately 60% of patients without diabetes develop stress hyperglycemia, defined as a blood glucose greater than 140 mg/dL.^{5–7}

Numerous studies have reported that, in critically ill and cardiac surgery patients, those who develop hyperglycemia are at increased risk for morbidity and mortality.^{7–16} Perioperative hyperglycemia, in patients with and without diabetes, is associated with higher rates of wound infections, acute renal failure, longer hospital stay, and higher perioperative mortality compared with those without hyperglycemia.^{8–13} Patients without diabetes who develop stress hyperglycemia during CABG surgery¹⁴ or during intensive care unit (ICU) stay¹⁵ have worse outcomes compared with those with previous history of diabetes.

Stress hyperglycemia in patients without diabetes undergoing surgery has been associated with up to a 4-fold increase in complications and a 2-fold increase in death compared with patients with normoglycemia^{16–18} and to subjects with diabetes.^{16,19–24} Stress mediators, namely stress hormones and cytokines, and the central nervous system interfere with insulin secretion and action leading to increased hepatic glucose production and reduced glucose uptake in peripheral tissues.^{25,26} The adverse outcomes associated with hyperglycemia may be attributed to hyperglycemia-induced inflammatory and oxidative stress as well as its prothrombotic and vascular abnormalities. This article discusses the pathophysiology of stress-induced hyperglycemia, the impact of hyperglycemia on clinical outcomes, and

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strategies for the management of hyperglycemia and diabetes in cardiac surgery patients with and without a history of diabetes.

EPIDEMIOLOGY OF STRESS HYPERGLYCEMIA

Hyperglycemia, defined as a blood glucose level greater than 140 mg/dL, is common in critically ill and cardiac surgery patients, reported in 60% to 80% of cardiac surgery patients^{5–7} and in 40% to 60% of general ICU patients.^{24,27–29} Most critically ill and cardiac surgery patients with hyperglycemia have a previous diagnosis of diabetes.^{12,24} Most patients with diabetes experience worsening glycemic control due to the stress of surgery and anesthesia or the use of corticosteroids and nutritional support.³⁰ 40% to 60% of patients without a history of diabetes experience transient hyperglycemia due to the stress of surgery,^{31–33} which resolves in many patients at the time of discharge. A third group of patients with inpatient hyperglycemia includes those who are newly diagnosed during hospitalization.^{33–36} Thus, all patients admitted to the hospital should undergo laboratory glucose testing. Subjects without a history of diabetes with blood glucose greater than 140 mg/dL should have bedside point-of-care glucose testing.^{37–39} In patients with hyperglycemia, measurement of hemoglobin A_{1c} (HbA_{1c}) differentiates stress hyperglycemia from diabetes in those who were previously undiagnosed.^{32,33} The American Diabetes Association and Endocrine Society guidelines indicate that patients with hyperglycemia and an HbA_{1c} of 6.5% or higher can be classified as having diabetes.³⁷ It is important to emphasize, however, that despite a high specificity (100%), the HbA_{1c} cutoff of greater than 6.5% has a poor sensitivity (57%)³² and its use is limited in patients with hemoglobinopathies, recent blood transfusion, severe kidney or liver disease, high-dose of salicylates, pregnancy, and iron deficiency anemia.⁴⁰ It is important to identify and track patients with stress hyperglycemia, because up to 60% of patients may have confirmed diabetes after 1 year of follow-up.³²

REGULATION OF BLOOD GLUCOSE IN HEALTHY INDIVIDUALS AND DURING STRESS

Maintenance of normoglycemia is essential for normal physiology in the body and is maintained by dynamic, minute-to-minute regulation of endogenous glucose production from the liver and kidneys and of glucose utilization by peripheral tissues.^{25,30,31,41} Glucose production is accomplished by gluconeogenesis and glycogenolysis. Insulin as the main regulatory hormone inhibits hepatic glucose production and stimulates glucose uptake by peripheral tissues (Fig. 1). During prolonged fasting, a reduction in insulin concentration leads to increased lipolysis (fat breakdown) releasing glycerol and to proteolysis (protein breakdown) releasing lactate and amino acids (alanine) that serve as the most important gluconeogenesis precursors.⁴¹ Excess glucose is polymerized to glycogen, which is mainly stored in the liver and muscle. Glycogenolysis, mediated primarily by glucagon, breaks down glycogen to the individual glucose units for mobilization during times of metabolic need. These steps are dependent on the interaction between insulin and counter-regulatory hormones.²⁵

During stress, the release of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) antagonizes the action of insulin, leading to increased gluconeogenesis in the liver and impaired insulin action in peripheral tissues resulting in hyperglycemia. Glucagon excess counteracts the action of insulin on glucose metabolism by stimulating glycogenolysis and gluconeogenesis.⁴² Furthermore, catecholamines stimulate glucagon secretion and inhibit insulin release by pancreatic β -cells as well as suppression of glucose uptake in peripheral tissues.⁴³ High levels of circulating corticosteroids have been shown to increase gluconeogenesis and lipolysis and to inhibit insulin release.⁴⁴ Growth hormone increases hepatic glucose production and is known to cause insulin resistance in humans; however, its role during stress is less understood.⁴⁴

The normal response to stress is associated with activation of central nervous system and neuroendocrine axes with subsequent release of counter-regulatory hormones. These hormones modify the inflammatory response, especially cytokine release that results in several alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency. Acute stress increases proinflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin (IL)-6, and IL-1, resulting in increased insulin resistance by interfering with insulin signaling.⁴⁵ Thus, stress adversely affects multiple biological processes, resulting in diminished insulin action, and if the pancreas is unable to compensate by increasing insulin production, the result is the development of hyperglycemia. Furthermore, in the presence of hyperglycemia, the pancreatic β -cells develop desensitization (glucose toxicity) that results in further blunting of insulin secretion and increasing serum glucose levels.⁴⁶

Increasing evidence indicates that development of hyperglycemia leads to the generation of reactive oxygen species (ROS), which affect different biological signaling pathways.⁴⁷ ROS are formed from the reduction of molecular oxygen or by oxidation of water to yield products, such as superoxide anion, hydrogen peroxide, and hydroxyl radical. The mitochondria and NADPH oxidase system are the major sources of ROS production.⁴⁸ In moderate amounts, ROS are involved in several physiologic processes that produce desired cellular responses. Large quantities of ROS, however, can lead to cellular damage of lipids, membranes, proteins, and DNA. In addition, oxidative stress has also been implicated as a contributor to β -cell dysfunction and mitochondrial dysfunction, which can lead to the development and worsening of hyperglycemia.⁴⁹

CONSEQUENCES OF HYPERGLYCEMIA IN HOSPITALIZED PATIENTS

Although the underlying causes have not been completely elucidated, several mechanisms have been proposed to explain the higher risk of complications and mortality of hyperglycemia in critically ill patients (see Fig. 1). Severe hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate, and pre-renal azotemia. Hyperglycemia has been shown to increase rates of hospital infections and to impair collagen synthesis and wound healing among patients with poorly controlled diabetes.^{25,40,50} It is also associated with impaired leukocyte function, including decreased phagocytosis, impaired bacterial killing, and chemotaxis. In addition, acute hyperglycemia

results in nuclear factor κ B (NF- κ B) activation and production of inflammatory cytokines, such as TNF- α , IL-6, and plasminogen activator inhibitor-1, which cause increased vascular permeability and leukocyte and platelet activation.⁵¹ Furthermore, high glucose concentrations have deleterious effects on endothelial function by suppressing formation of nitric oxide and impairing endothelium-dependent flow-mediated dilation as well as abnormalities in hemostasis, including: increased platelet activation, adhesion, and aggregation and; reduced plasma fibrinolytic activity.⁵² Adding to the effects of hyperglycemia in acute coronary syndrome, high free fatty acid levels seen in diabetes and stress can also aggravate ischemia/reperfusion damage by limiting the ability of cardiac muscle to uptake glucose for anaerobic metabolism.^{25,53}

Several studies have shown that the hormonal and proinflammatory aberrations associated with stress hyperglycemia return to normal after treatment with insulin and resolution of hyperglycemia.⁴⁵ The anti-inflammatory and antihyperglycemic effects of insulin are well established.^{54,55} Insulin acts to suppress counter-regulatory hormones and proinflammatory transcription factors and may even suppress the formation of reactive oxidation species.⁵⁶ Insulin suppresses major proinflammatory transcription factors: NF- κ B, , activator protein 1, and early growth response 1. Correction of hyperglycemia has been shown to improve the inflammatory response and to reduce generation of ROS (including superoxide radical) generation.^{56,57} In addition, insulin induces vasodilation and inhibits lipolysis and platelet aggregation. The vasodilation that accompanies insulin administration may be attributed to its ability to stimulate nitric oxide release and induce the expression of endothelial nitric oxide synthase.⁵⁸ The impaired lipolysis and reduction in free fatty acids that accompany insulin administration may be associated with decreases in thrombosis and inflammation.⁵³

EVIDENCE FOR CONTROLLING PERIOPERATIVE HYPERGLYCEMIA IN CARDIAC SURGERY PATIENTS

The negative impact of hyperglycemia in patients admitted for cardiac surgery merits a comprehensive and multidisciplinary approach. This plan should include dietary modifications, glucose monitoring, personalized glycemic targets to improve hyperglycemia while preventing hypoglycemia, a safe transitioning plan from the ICU to the regular floors and/or home, and proper outpatient follow-up.^{39,59,60}

Intraoperative Period

In a retrospective study of 409 patients undergoing cardiac surgery, Gandhi and colleagues⁶¹ reported that for each incremental increase in intraoperative glucose by 20 mg/dL above 100 mg/dL, there was a 30% increase in occurrence of adverse events, including pulmonary and renal complications and death. In contrast to this retrospective study, a randomized controlled trial of 400 diabetic and nondiabetic surgery patients assigned to receive continuous insulin infusion (CII) to maintain intraoperative glucose level between 80 mg/dL and 100 mg/dL versus a glucose target less than 200 mg/dL reported no improvement in clinical outcome or complications.⁶² A meta-analysis of 5 randomized controlled trials in 706 cardiac surgery patients reported that rigorous intraoperative glycemic control decreased the infection rate compared with the conventional therapy but did not decrease mortality.⁶³

Postoperative Period

Several randomized controlled trials in cardiac surgery patients have evaluated the impact of hyperglycemia and ideal blood glucose target during the postoperative period to optimize outcomes.^{14,64–68} Desai and colleagues⁶⁴ randomized 189 patients to an intensive target of 90 mg/dL to 120 mg/dL and to a conventional target between 121 mg/dL and 180 mg/dL in first-time CABG surgery patients. They reported no differences in deep sternal wound infection, pneumonia, perioperative renal failure, or mortality. Similarly, Pezzella and colleagues⁶⁷ and Lazar and colleagues⁶⁵ reported no differences in perioperative complications, hospital length of stay, and mortality between intensive insulin targeting glucose of 90 mg/dL to 120 mg/dL versus 120 mg/dL to 180 mg/dL. In a recent study, Umpierrez and colleagues¹⁴ aimed to determine if the lower end of the recommended glucose target can reduce hospital complications in patients undergoing CABG surgery randomized patients with hyperglycemia to an intensive insulin therapy aimed to maintain a blood glucose between 100 mg/dL and 140 mg/dL or to a conservative therapy aimed to maintain a glucose value between 141 mg/dL and 180 mg/dL in an ICU.¹⁴ The primary outcome of this trial was to determine differences between a composite of complications, including wound infection, pneumonia, bacteremia, acute kidney injury, major adverse cardiovascular events, and mortality. The authors found no differences in a composite of complications (42% vs 52%, $P = .08$). The authors observed, however, heterogeneity in treatment effect according to diabetes status, with no differences in complications among patients with prior history of diabetes treated with intensive or conservative regimens (49% vs 48%, $P = .87$) but a significantly lower rate of complications in patients without diabetes treated with an intensive treatment regimen compared with the conservative treatment regimen (34% vs 55%, $P = .008$). In agreement with these findings, a recent study by Blaha and colleagues⁶⁸ in 2383 cardiac surgery patients treated to a target glucose range between 80 mg/dL and 110 mg/dL reported a reduction in postoperative complications only in nondiabetic patients (21% vs 33%; relative risk, 0.63; 95% CI, 0.54–0.74), whereas no significant benefit of intensive therapy was seen in patients with diabetes. Moreover, a subgroup analysis by Van den Berghe and colleagues⁶⁹ of surgical and medical ICU patients reported that whereas glucose lowering effectively reduced mortality in those without a previous history of diabetes, no significant benefit from treatment was observed in patients with diabetes.

Clinical guidelines on inpatient management of hyperglycemia recommend the use of IV CII in critically ill and in cardiac surgery patients with and without a history of diabetes.^{37,39,60,70,71} Several cohort and randomized controlled trials in cardiac surgery patients have reported that improvement in glycemic control can reduce short-term and long-term complications and hospital mortality.^{14,68,72,73} A target glucose level between 140 mg/dL and 180 mg/dL is recommended for most ICU and cardiac surgery patients with hyperglycemia and diabetes, but lower targets between 110 mg/dL and 140 mg/dL could be appropriate in a select group of ICU patients (ie, centers with extensive experience and cardiac surgical patients).³⁹ Recent studies in mixed ICU populations and in cardiac surgery patients have shown that intensive insulin therapy (glucose target <110 mg/dL) does not reduce complications compared with conventional control but increases the risk of hypoglycemia.^{65,74}

Table 1 presents a comprehensive review of observational and prospective randomized trials addressing intensive glycemic control in patients undergoing cardiac surgery.^{14,62,64–68,72,73,75–78} Although the readers should use caution with extrapolating data from the medical or surgical ICUs and combined trials into the cardiothoracic ICU practice, the overall consensus is that hyperglycemia management, targeting less stringent goals (140–180 mg/dL), represents the standard of care in hospitalized patients.^{38,39,59,60,79}

MANAGEMENT OF PERIOPERATIVE HYPERGLYCEMIA DURING CARDIAC SURGERY

Management of Hyperglycemia in Intensive Care Unit Settings

Insulin therapy is effective in achieving and maintaining glycemic control in patients with diabetes and with stress hyperglycemia in an ICU.^{25,38,39,60} Several protocols have been published, both nursing-driven and computer-generated algorithms, which have been validated for their safety and efficacy.^{80–82}

There is no ideal protocol for the management of hyperglycemia in the critical patient. In addition, there is no clear evidence demonstrating the benefit of one protocol/algorithm versus another. Most institutions have standard nursing-driven protocols to facilitate insulin titration and to avoid errors in insulin dosing. Essential elements that increase protocol success are (1) rate adjustment that considers the current and previous glucose values and the current rate of insulin infusion, (2) rate adjustment that considers the rate of change (or lack of change) from the previous reading, and (3) frequent glucose monitoring (hourly until stable glycemia is established and then every 2–3 hours). Several computer-based algorithms aiming at directing the nursing staff adjusting insulin infusion rate have become commercially available (Glucomander [Glytec, Greenville, South Carolina], EndoTool System [MD Scientific, Charlotte, North Carolina], GlucoStabilizer [Medical Decision Network, Charlottesville, Virginia], and GlucoTab [Joanneum Research, Graz, Austria, and Medical University of Graz, Graz, Austria]).⁸³ These devices may be especially useful in hospitals with no diabetes management teams or diabetes experts on staff; however, some come at a considerable financial cost to institutions. Table 2 shows an example of the authors' paper-based IV insulin infusion and hypoglycemia protocol. This protocol was specifically developed to be used in cardiac surgery ICU patients in the authors' hospitals.

It has been shown that glucose targets are usually achieved with most protocols within approximately 4 hours.⁸⁴ The onset of regular insulin after IV administration is within 15 minutes to 30 minutes, with a half-life of approximately 9 minutes and duration of action between 30 minutes and 60 minutes. These features allow a rapid up-titration or down-titration of insulin rate in anticipated (ie, rapid decline of blood glucose and use of vasopressors) or unanticipated (ie, acute clinical status deteriorations and hypoglycemia) situations.^{60,81,82} Insulin infusion requirements are usually higher during the first few hours of infusion in patients with severe hyperglycemia. Postoperative stress, pain, presence of infection or administration of pressors are factors that have an impact on insulin requirements.⁸² Thus, it is recommended to monitor glucose values every 1 hours to 2 hours and to adjust insulin infusion rates accordingly.⁸⁵ Insulin infusion should be continued until

clinical and hemodynamic stability has been achieved, until patients are tolerating oral intake or receiving nutritional support, and after several hours of stable glycemic control.

Management of Hyperglycemia in Non-intensive Care Unit Settings

Subcutaneous insulin is the preferred therapeutic agent for glucose control in cardiac surgery patients after stopping CII or after transition to non-ICU areas. Transition to subcutaneous insulin should be considered in hemodynamically stable patients who are off pressors and are tolerating oral intake.⁸² Use of protocols for insulin transition leads to better glucose control than nonprotocol therapy, with lower rates of complications and hypoglycemia. A protocol-based transition to a subcutaneous regimen, using basal insulin early after initiation of CII, has also been shown to decrease rebound hyperglycemia after infusion discontinuation.⁸⁶

The basal-bolus (or basal-prandial) insulin regimen is considered the physiologic approach because it addresses the 3 components of insulin requirement: basal (required in the fasting state), nutritional (required for peripheral glucose disposal following a meal), and supplemental (required for unexpected glucose elevations or for disposal of glucose in hyperglycemia).^{37,39,60} In insulin-naïve patients, the calculation of basal and bolus insulin dosing requirements should be based on a patient's previous rate of IV insulin infusion and carbohydrate intake.^{82,85} Due to the short IV insulin half-life, administration of the initial subcutaneous basal dose is recommended at least 2 hours to 4 hours before stopping the insulin infusion to prevent rebound hyperglycemia.

Most nondiabetic patients with stress hyperglycemia requiring less than 1 U/h to 2 U/h frequently do not require transition to scheduled subcutaneous basal-bolus therapy but rather just correctional insulin scale. Those requiring insulin infusion at a rate of greater than 2 U/h can be started to at 50% of the calculated 24-hour insulin requirements. Most patients with a history of diabetes, however, require transition to subcutaneous insulin therapy. Patients with type 2 diabetes mellitus can be started at 80% of the calculated daily IV insulin requirements.^{87–89} The total insulin dose is given 50% as basal and 50% as bolus (prandial) insulin.^{82,85,90–92}

Several randomized controlled trials using subcutaneous basal or basal-bolus insulin regimens have been shown successful and are preferred over the use of sliding-scale insulin alone in hospitalized patients with type 2 diabetes mellitus.^{93–95} Basal insulin analogs, such as glargine and detemir, are generally preferred over NPH insulin or premixed insulin, because the latter has been associated with lower glycemic variability and less severe hypoglycemia.^{96,97} Recently, a study comparing the 2 most commonly used basal insulins, glargine and detemir, in the management of inpatient hyperglycemia and diabetes reported similar efficacy in glycemic control and hypoglycemia rates between these 2 insulin formulations.⁹⁸ Renal dysfunction, a common complication in hospitalized patients, increases the risk of insulin and non-insulin-related hypoglycemia.⁹⁹ Baldwin and colleagues¹⁰⁰ studied 2 basal-bolus (glargine-glulisine) insulin-dosing regimens in hospitalized patients with diabetes and chronic kidney disease (estimated glomerular filtration rate <45 mL/min). The investigators found that a weight-based insulin regimen of 0.25 U/kg/d was associated with 50% less hypoglycemia (15.8% vs 30%, $P = .08$) compared

with a traditional approach of a total daily dose of 0.5 U/kg. In patients with reduced oral intake, the administration of a single dose of basal once-daily dose plus correctional premeal doses of rapid-acting insulin per sliding scale (basal-plus approach) may be an alternative to basal-bolus regimen.¹⁰¹

GLUCOSE MONITORING DURING THE PERIOPERATIVE PERIOD

All patients with a diagnosis of diabetes and those with newly discovered hyperglycemia should be monitored closely during the perioperative period. The frequency of monitoring and the schedule of the blood glucose checks are dependent on the nutritional intake, patient treatment, and schedule of insulin. Current guidelines recommend glucose monitoring every 1 hour to 2 hours in critically ill patients receiving IV insulin administration.⁶⁰ There is some controversy regarding the best method to monitor blood glucose. A recent international consensus meeting recommended against relying solely on the use of capillary blood glucose, given the poor reliability of meters in critically ill patients.¹⁰² In patients with permanent vascular access (arterial and/or venous), samples for glucose monitoring could be easily drawn after standard safety precautions. Arterial catheters may be preferred in patients with shock, severe peripheral edema, and/or on vasopressor therapy.¹⁰² Considering the convenience and wide availability, however, capillary point-of-care testing is the most widely used approach in the hospital setting. When using point-of-care testing, clinicians should account for conditions that might alter the meter accuracy of glucose measurement, such as hemoglobin level, perfusion, and medications. In addition, safety standards should be established for blood glucose monitoring that prohibits the sharing of finger-stick lancing devices, lancets, and needles.³⁰

The use of continuous glucose monitoring (CGM) has been proposed as an alternative to capillary glucose testing in the hospital setting.^{103–107} CGM provides frequent measurements of glucose levels as well as direction and magnitude of glucose trends facilitating short and long-term therapy adjustments and limiting glycemic excursions. CGM devices can sample glucose intravascularly (venous or arterial blood) or subcutaneously by way of interstitial fluid.¹⁰⁴ CGM devices can be highly invasive (intravascular devices), minimally invasive (subcutaneous), or even noninvasive (transdermal). Sampling and measurement frequencies typically range from 1 minute to 15 minutes, but most commonly are done every 5 minutes. There are currently 5 CGMs approved for use in Europe and 1 CGM system approved by the Food and Drug Administration for use in US hospitals.¹⁰⁴ Although the use of CGM in the ICU population has the potential for improving glucose control from an accuracy standpoint, there are several concerns. Technological limitations that impede accuracy of CGMs include buildup of tissue deposits (biofilm), the need for regular calibration due to sensor drift, measurement lag, and substance interference (acetaminophen, maltose, ascorbic acid, dopamine, mannitol, heparin, uric acid, and salicylic acid). In addition, the intravascular CGM devices carry the risk of thrombus formation, catheter occlusion, and catheter-related infections.¹⁰⁸

HYPOGLYCEMIA AND OUTCOMES IN PATIENTS HOSPITALIZED WITH CARDIAC CONDITIONS

Hypoglycemia (<70 mg/dL) is the most common adverse event associated with insulin administration^{99,109–111} and has been associated with poor clinical outcomes and higher mortality.^{74,112} Hypoglycemia is associated with increased risk of arrhythmias, ranging from bradycardia to ventricular ectopic beats and QT prolongation, mostly because of sympathetic and adrenal activation.¹¹³ The relationship between mortality and glycemic control in hospitalized patients with acute cardiovascular disease follows a U-shape curve,^{114–116} with a 2-fold increase in mortality in patients with hypoglycemia.⁷⁴ In the NICE-SUGAR (The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trial, the adjusted hazard ratios for death among patients with moderate (<70 mg/dL) or severe (<40 mg/dL) hypoglycemia, compared with those without hypoglycemia, were 1.41 (95% CI, 1.21–1.62; $P<.001$) and 2.10 (95% CI, 1.59–2.77; $P<.001$), respectively. Several studies have reported that spontaneous hypoglycemia is associated with worse outcomes and higher mortality than iatrogenic hypoglycemia in hospitalized patients,^{110,111,114} suggesting that spontaneous hypoglycemia may be a marker of disease severity. Because hypoglycemia may go unrecognized in patients under anesthesia or those who are critically ill,³⁰ frequent glucose monitoring, conservative glucose targets, excellent perioperative provider communication, and treatment algorithms are needed to reduce the risk of intraoperative and postoperative hypoglycemia.

MANAGEMENT OF DIABETES AFTER HOSPITAL DISCHARGE

The transition of care from inpatient to the outpatient settings has been determined as a national priority in patients with diabetes.¹¹⁷ The Joint Commission National Patient Safety Goals document includes goals and requirements for hospital discharge planning and transitional care. Hospital discharge represents an opportune time to address glycemic control and to adjust home diabetes therapy if necessary. Few studies, however, have focused on the optimal management of hyperglycemia and diabetes after hospital discharge. Clinical guidelines have recommended that patients with diabetes and hyperglycemia have an HbA_{1c} measured to assess preadmission glycemic control and to tailor treatment regimen at discharge. In a recent randomized control trial, the authors' group validated a discharged patient algorithm based on admission HbA_{1c}, as shown in Fig. 2. Patients with acceptable diabetes control (HbA_{1c} <8%) may be discharged on their prehospitalization treatment regimen (oral agents and/or insulin therapy). Patients with suboptimal glucose control and HbA_{1c} between 8% and 10% should have intensification of therapy, either by adding or increasing the dose of oral agents or by adjusting the dose of basal insulin (approximately 50%). Those with HbA_{1c} greater than 10% should be considered candidates for insulin therapy alone (basal-bolus) or in combination to oral agents.¹¹⁸ When a patient is discharged from the hospital with poorly controlled diabetes or with insulin therapy, a clear strategy for the management of hyperglycemia and hypoglycemia, and a titration of therapy should be communicated to the community diabetes team and/or primary care team.

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KEY POINTS

- Perioperative hyperglycemia is common after cardiac surgery and is associated with higher health care resource utilization, longer length of stay, and greater perioperative mortality.
- Improvement in glycemic control, in patients with stress hyperglycemia and diabetes, has a positive impact on morbidity and mortality.
- A target blood glucose level between 140 mg/dL and 180 mg/dL is recommended for most patients during the perioperative period.
- Insulin given by continuous insulin infusion is the preferred regimen for treating hyperglycemia in critically ill patients.
- Subcutaneous administration of basal bolus or basal plus correctional bolus is the preferred treatment of non-critically ill patients.

Fig. 1.
Mechanism of stress hyperglycemia and its complications in surgical patients.

Fig. 2.

Hospital discharge algorithm based on admission HbA_{1c} (A1C). OAD, oral antidiabetic drugs. (*Adapted from Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA_{1c} for the management of patients with type 2 diabetes. Diabetes Care 2014;37(11):2934–9; with permission.*)

Table 1

Studies of intensive glycemic control in cardiac surgery populations

Study	Patients	Population	Target Blood Glucose (mg/dL)	Clinical Outcomes
Fumary et al, ⁷⁶ 1999	N = 2467 I: 1499 (CII) C: 968 (subcutaneous)	DM Cardiac surgery 85% CABG	I: 150–200 C: >200	65% reduction in risk of deep sternal wound infections
Van den Berghe et al, ⁷² 2001	N = 1548 I: 544 C: 557	DM and no-DM 62% cardiac surgery 57% CABG 13% DM	I: 80–110 C: 180–200	32% reduction in adjusted mortality risk
Fumary et al, ⁷³ 2003	N = 3554 I: 2612 C: 942	DM CABG	Variable: <200 before 1991, 150–200 between 1991–1998, 125–175 between 1999 and 2001 and between 100 and 150 after 2001	50% reduction in adjusted mortality risk
Lazar et al, ⁶⁶ 2004	N = 141 I: 72 C: 69	DM CABG	I: 125–200 C: <250	60% reduction in postoperative atrial fibrillation
Ingels et al, ⁷⁷ 2006	N = 970 C: 477 I: 493	DM and no-DM Cardiac surgery <20% DM	I: <110 C: <220	41% reduction in unadjusted mortality risk at 2 y and 22% at 3 y No significant (12.7%) reduction at 4 y
Li et al, ⁷⁸ 2006	N = 93	DM	I: 150–200	No differences in mortality, wound infections, or ICU LOS

Study	Patients	Population	Target Blood Glucose (mg/dL)	Clinical Outcomes
	C: 42 I: 51	CABG	C: 150–200	
Gandhi et al, ⁶² 2007	N = 371 C: 185 I: 186	DM and no-DM, Cardiac surgery Approximately 20% DM	I: 80–100 C: <200	No significant differences in mortality or morbidity
Chan et al, ⁷⁵ 2009	N = 99 C: 55 I: 54	DM and no-DM, Cardiac surgery Approximately 30% DM Approximately 34% CABG	I: 80–130 C: 160–200	No differences in 30-d mortality
Lazar et al, ⁶⁵ 2011	N = 82 C: 42 I: 40	DM CABG	I: 90–120 C: 120–180	No differences in 30-d mortality, myocardial infarction, stroke, infection, atrial fibrillation, ventilator time, ICU LOS
Desai et al, ⁶⁴ 2012	N = 189 C: 82 I: 107	DM and no-DM CABG Approximately 41%–45% DM	I: 90–120 C: 121–180	No differences in deep sternal wound infections, pneumonia, renal failure, or mortality
Pezzella et al, ⁶⁷ 2014	N = 189 C: 98 I: 91	DM and no-DM CABG Approximately 41%–45% DM	I: 90–120 C: 121–180	No differences in perioperative complications No differences in mortality at 40 mo of follow-up
Blaha et al, ⁶⁸ 2015	N = 2383 C: 1134 I: 1249	DM and no-DM Cardiac surgery Approximately 70% CABG	I: 80–110 C: 80–150	37% reduction in risk of postoperative complications in no-DM No differences in complications in DM

Study	Patients	Population	Target Blood Glucose (mg/dL)	Clinical Outcomes
Approximately 23%–27% DM				
Umpierrez et al. ¹⁴ 2015	N = 338	DM and no-DM	I: 100–140	62% reduction in risk of postoperative complications in no-DM
	C: 151	CABG	C: 141–180	
	I: 151	50% DM		No difference in complications in DM

Abbreviations: BG, blood glucose; C, control/conventional treatment group; DM, diabetes mellitus; I, intervention/intensive treatment group; LOS, length of stay; N, number of patients; no-DM, no history of DM.

Table 2

Emory healthcare protocol for intravenous insulin infusion in critically ill patients undergoing cardiothoracic surgery with hyperglycemia

Initiating the insulin drip			
History of diabetes or $HbA_{1c} > 6.5\%$: begin insulin drip with first BG > 180 mg/dL			
No history of diabetes and $HbA_{1c} < 6.5\%$: begin if BG > 180 mg/dL $\times 2$ consecutive occasions			
Calculating initial IV insulin infusion rate			
BG/100 = U/h (round to the nearest 0.1; U/h = mL/h)			
Target range: 110–140 mg/dL			
Adjusting the insulin drip			
<i>Blood glucose (mg/dL)</i>	<i>Any increase in blood glucose from prior blood glucose</i>	<i>Blood glucose decrease less than 30 mg/dL from prior blood glucose</i>	<i>Blood glucose decrease greater than 30 mg/dL from prior blood glucose</i>
> 241	Increase rate by 3 U/h	Increase rate by 3 U/h	No change
211–240	Increase rate by 2 U/h	Increase rate by 2 U/h	No change
181–210	Increase rate by 1 U/h	Increase rate by 1 U/h	No change
141–180	Increase rate by 0.5 U/h	Increase rate by 0.5 U/h	No change
110–140	No change	No change	Decrease rate by 50%
91–109	Decrease rate by 50%	Decrease rate by 50%	<ol style="list-style-type: none"> 1 HOLD insulin drip 2 Check BG every 1 h 3 Restart infusion rate at 50% of prior insulin rate when BG > 140 mg/dL
71–90	<ol style="list-style-type: none"> 1 HOLD insulin drip 2 Check BG every 30 min, when BG > 90 mg/dL, check BG every hour 3 Restart infusion rate at 50% of prior insulin rate when BG > 140 mg/dL 		

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70 or less	<div><div>1</div><div>HOLD insulin drip and ADMINISTER IV dextrose 50% as follows:</div></div>
	<div><div>2</div><div>If BG 41–70 mg/dL: give half ampule of dextrose 50% IV or 235 mL of juice PO</div></div>
	<div><div>3</div><div>If BG 40 mg/dL: give 1 ampule of dextrose 50% IV</div></div>
	<div><div>4</div><div>Repeat BG every 15 min until BG >70 mg/dL, then every 30 min until BG >90. When BG >90 mg/dL, check BG every 1 h</div></div>
	<div><div>5</div><div>Restart infusion at half of prior infusion rate when BG >140 mg/dL</div></div>