

Lowering Glucose to Prevent Adverse Cardiovascular Outcomes in a Critical Care Setting

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Lowering Glucose to Prevent Adverse Cardiovascular Outcomes in a Critical Care Setting

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High admission blood glucose levels after acute myocardial infarction are common and associated with an increased risk of death in patients with or without diabetes. Hyperglycemia is associated with altered myocardial blood flow and energetics and can lead to a pro-oxidative/proinflammatory state. The use of intensive insulin treatment has shown superior benefits in the treatment of hyperglycemia versus glucose-insulin-potassium infusion, particularly in critical care settings. (J Am Coll Cardiol 2009;53:S9-13) © 2009 by the American College of Cardiology Foundation

In recent years, attention has been given to evidence that in patients admitted to the intensive care unit (ICU) with acute coronary syndrome (ACS), hyperglycemia is associated with an increased risk of mortality and morbidity, in the presence or absence of a history of diabetes (1). Frequently in medicine, the “new” discovery of an old finding occurs; hyperglycemia in ACS is one of these cases. An unusually high prevalence of glycosuria in acute myocardial infarction (AMI) patients without diabetes was noted as early as 1931 (2). However, the observation that fasting blood glucose levels shortly after myocardial infarction are a better guide to prognosis was not reported until 1975 (3). Associations linking hyperglycemia during ACS and subsequent mortality were reported in 1987 (4) and confirmed in 1989 (5), 1991 (6), and 1993 (7). A large meta-analysis by Capes et al. (1) in 2000 further addressed this issue, adding to the evidence that lowering glucose decreases mortality in patients with diabetes in the presence of ACS (8). This meta-analysis of 15 cohort studies and clinical trials involving 1,856 patients without diabetes hospitalized for AMI found that those with blood glucose levels >110 to 144 mg/dl had a 3.9-fold (95% confidence interval [CI]: 2.9 to 5.4) greater risk of death than those with lower levels. Those with glucose levels >144 to 180 mg/dl were also at increased risk for heart failure and cardiogenic shock (1).

In some cases, the elevation of glucose could simply be a marker of pre-existing, but not yet detected, type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (9). Norhammar et al. (9) reported on a cohort with a mean age of 63.5 ± 9 years and a mean blood glucose concentration at admission of 117 mg/dl. The mean 2-h post-load blood glucose concentration was 166 mg/dl at hospital discharge, and 162 mg/dl 3 months later. The numbers of individuals who had impaired glucose tolerance at discharge and after 3 months were 58 of 164 (35%, 95% CI: 28% to 43%) and 58 of 144 (40%, 95% CI: 32% to 48%), respectively, and those with previously undiagnosed T2DM were 51 of 164 (31%, 95% CI: 24% to 38%) and 36 of 144 (25%, 95% CI: 18% to 32%). Independent predictors of abnormal glucose tolerance at 3 months were concentrations of hemoglobin A1C at admission ($p = 0.024$) and fasting blood glucose concentrations 4 days after admission ($p = 0.044$). These results suggested that previously undiagnosed diabetes and impaired glucose tolerance were common in patients with AMI and that these abnormalities may be detected early. A positive association between hyperglycemia at the time of the event and subsequent mortality from ACS, even in patients without diabetes, has been frequently and recently confirmed (10–13).

Factors Contributing to Poor Prognosis

Although stress hyperglycemia correlates well with prognosis in ACS, the correlation between admission glucose levels and infarct size, as measured by myocardial enzyme release, has not been universal (11). Thus, excessive stress-mediated release of counter-regulatory hormones (i.e., catecholamines, glucagon, and cortisol) caused by a greater degree of myocardial damage cannot fully account for the extent of hyperglycemia in ACS. Other pathophysiological mechanisms involved in the excess mortality in patients with AMI and acute hyperglycemia need to be identified. The links among

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**Abbreviations
and Acronyms**

ACS = acute coronary syndrome
AMI = acute myocardial infarction
ATP = adenosine triphosphate
CABG = coronary artery bypass grafting
CI = confidence interval
CV = cardiovascular
FFA = free fatty acid
GIK = glucose-insulin-potassium
ICU = intensive care unit
SPRINT = Specialized Relative Insulin and Nutrition Tables
T2DM = type 2 diabetes mellitus

obesity, insulin resistance, diabetes, and cardiovascular (CV) disease may help us to better understand both the prevalence of hyperglycemia in ACS and the association of hyperglycemia with adverse CV outcomes. Insulin-resistant patients with ACS are more prone to hyperglycemia in the setting of acute stress caused by relative insulinopenia, which is mediated, in part, by a decrease in pancreatic beta-cell function and increased hepatic glycogenolysis, as well as insulin resistance exacerbated by increased free fatty acid (FFA) levels (14). Insulin resistance is associated with a host of traditional (i.e., obesity, hypertension, glucose intolerance, microalbuminuria, and atherogenic dyslipidemia) and novel (i.e., endothelial dysfunction and proinflammatory, pro-oxidative, and prothrombotic states characterized by abnormal levels of circulating adhesion molecules, cytokines, and adipokines, such as adiponectin) CV risk factors. These same factors are also associated with increased CV events, as well as an adverse prognosis in ACS.

In the San Antonio Heart Study, high levels of insulin resistance were associated with a 2.5-fold increased risk of developing CV events (15). Interestingly, after adjusting for 11 known CV risk factors, insulin-resistant subjects still had a 2-fold increased risk of CV disease. Thus, insulin resistance was associated with excess CV risk independent of associated metabolic risk factors.

Additionally, acute hyperglycemia is associated with adverse metabolic effects that may contribute to a poor outcome in ACS. Although glucose metabolism is a major myocardial energy source, it is important to recognize that oxidation of FFAs is the preferred source of energy in the resting aerobic state. Myocardial ischemia results in an increased rate of glycogen breakdown and glucose uptake via translocation of glucose transporter-4 receptors to the sarcolemma (16). This adaptive mechanism is important because glucose oxidation requires less oxygen than FFA oxidation to maintain adenosine triphosphate (ATP) production. Thus, myocardial energetics are more efficient during the increased dependence on glucose oxidation with ischemia. With relative insulinopenia (insulin resistance or frank diabetes) exacerbated by the stress of ACS, the ischemic myocardium is forced to utilize FFAs more than glucose for an energy source because myocardial glucose uptake is acutely impaired. Thus, despite acute hyperglycemia, a metabolic crisis may ensue as the hypoxic myocardium becomes less energy efficient in the setting of frank

diabetes or insulin resistance, as FFA oxidation results in the generation of fewer ATP molecules per molecule of oxygen as compared with glucose oxidation. Catecholamine release with stress further stimulates the release of FFAs, which may contribute to myocardial damage and arrhythmia risk by increasing oxygen demand and oxidative stress (17,18).

The adverse effects of acute hyperglycemia may also be, in part, attributable to the direct effects of elevated glucose levels on the blood vessel wall and on platelet function, which are discussed by Dandona et al. (19) elsewhere in this Supplement.

**Insulin Treatment in the ICU:
Need for a Standard Validated Algorithm**

Tight glycemic control is an important issue in the management of ICU patients and in particular to the cardiologist. The glycemic goals described by Van den Berghe et al. (20) in their landmark study of intensive insulin therapy seem difficult to achieve in the ICU setting. Many CV specialists are concerned about the increased frequency of severe hypoglycemic episodes with more stringent glycemic control, and several protocols have been proposed to address these concerns. A recent small observational study evaluated adherence, efficacy, and safety of an insulin protocol for critically ill patients with target blood glucose levels between 81 and 110 mg/dl; factors associated with adequate daily blood glucose control were also examined (21). Blood glucose measurements were obtained during 352 protocol implementation days; with 71% adherence, glucose levels were within the desired range 42% of the time, and 60% of patients experienced at least 1 hypoglycemic event. Adherence to the protocol ($p < 0.001$), high bilirubin level ($p < 0.001$), low daily insulin dose ($p = 0.002$), and low C-reactive protein level ($p = 0.048$) were independently associated with adequate daily blood glucose control. Protocol adherence was positively associated with daily time in the target range; however, efficacy during the total protocol implementation time remained poor. Because of the frequency of hypoglycemia, the investigators suggest that protocols to maintain blood glucose levels between 81 and 110 mg/dl in critically ill patients may not be recommended (21). Although this position is in the minority, it reflects the lack of consensus regarding the aim of insulin therapy; CV specialists must weigh the risk of hypoglycemia against the importance of obtaining good glycemic control.

Although hypoglycemia is unlikely to influence CV outcomes (22–24), a consensus regarding a universal standard insulin protocol has not been reached. The Specialized Relative Insulin and Nutrition Tables (SPRINT) protocol is a simple alternative ICU protocol for modulating insulin and nutritional input to gain tight blood glucose control in the 72 to 110 mg/dl target band (25). The tables were used by nurses to determine glycemic control actions based on hourly or 2-h blood glucose measurements and nutrition

and insulin administration rates. A pilot study using the SPRINT protocol was conducted, observing 2,152 h of blood glucose level control. Results showed that the patient cohort average Acute Physiology and Chronic Health Evaluation II score, a classification system to assess severity of disease, was higher compared with previous intensive insulin clinical studies (25). Overall, 64% of measurements were in the 72 to 110 mg/dl band, 89% in the 72 to 126 mg/dl band, and 96% in the 72 to 140 mg/dl band, with an average value of 105 mg/dl. Only 1.4% of all measurements were <72 mg/dl, with a minimum value of 58 mg/dl and a maximum value of 213 mg/dl. Glucose control was achieved using the SPRINT protocol, the results of which led to a high level of support and acceptance of frequent measurements required for effective glucose control. Moreover, because the protocol was easy to implement, minimal noncompliance by the clinical staff resulted (25).

The feasibility of insulin infusion therapy has been recently supported by a review of published trials using insulin/glucose algorithms in critically ill patients (26). Nine recent studies were conducted in the ICU, 9 other studies were conducted in the perioperative setting, and 6 studies were conducted in patients with AMI or stroke. Studies conducted before 2001 did not include normoglycemia among their aims. This changed after the landmark study by Van den Berghe *et al.* (27) in 2001, and glycemic goals became tighter, with a target range between 72 and 144 mg/dl in most subsequent studies. The use of a dynamic scale protocol with tight glucose targets and 2 blood glucose values to determine the insulin infusion rate seemed to yield the best results in terms of glycemic control and fewer hypoglycemic episodes (26).

Therapeutic Prospects/Options

Because glucose exerts several direct and powerfully damaging effects, all capable of worsening prognosis after ACS, important questions for CV specialists remain: 1) Should hyperglycemia, in the presence of ACS, be treated with glucose-insulin-potassium (GIK)? 2) Should hyperglycemia in ACS be treated with intensive insulin therapy alone? 3) How should hyperglycemia in ACS be treated in patients without diabetes?

Evidence From Critical Care Settings

Strong support for tight glycemic control as a key strategy for improving prognosis after ACS comes from the study by Van den Berghe *et al.* (27). This prospective trial studied 1,548 patients in a surgical ICU who stayed more than 5 days. One-half of the patients were infused with insulin and thus rendered relatively euglycemic (fasting blood glucose 80 to 110 mg/dl). A reduction in total mortality (48%), incidence of bacteremia (46%), renal failure requiring dialysis (41%), intensive care neuropathy (44%), and the need for red blood cell transfusion (50%) occurred, compared with control subjects. Moreover, the need for mechanical

ventilation and intensive care was also reduced in these patients (27). These results highlighted the message that outcomes, which improve with low-dose insulin infusion, are more dependent on the reduction in plasma glucose levels than on the dose of insulin administered (28).

In a prospective study designed to reduce and maintain glucose concentrations <110 mg/dl in a medical ICU population requiring admission for >3 days, insulin therapy reduced mortality by 18% and reduced the duration of mechanical ventilation and incidence of renal injury compared with control subjects (20). Other benefits included a reduction in the length of stay in the ICU and the hospital. These findings were consistent with an observation by Krinsley (29) in a similar setting, the medical ICU of a community teaching hospital.

Evidence From ACS Trials

A number of recent clinical trials of insulin therapy in the setting of ACS have been conducted (Table 1) (30–36). Reduction in mortality was not consistently shown. However, in 1 of these trials (36), subgroup analysis showed a reduction in C-reactive protein in patients receiving insulin therapy (37). The investigators reported that in patients with or without known diabetes with hyperglycemia during MI, it is important to maintain normoglycemia with insulin infusion in the first 24 h during MI, which tends to be accompanied by a significantly smaller increase of C-reactive protein. Interestingly, the investigators found a positive correlation between mean glucose levels during the first 24 h and serum C-reactive protein levels 2 days after admission. However, this correlation was found only when the control and treatment groups were pooled; no correlation was found with the insulin dose. Therefore, although this report is of great interest, the question regarding the major usefulness of insulin infusion versus tight glycemic control was not answered (38).

Finally, another recent study using GIK infusion at the time of reperfusion with thrombolytic agents (3 h after chest pain) showed an 88% reduction in major CV events at 1 year (39). However, these results require more study.

Evidence From Cardiac Surgery

The importance of reducing glucose concentrations in patients undergoing coronary artery bypass grafting (CABG) has been shown in retrospective and prospective controlled studies by Furnary *et al.* (40) and Lazar *et al.* (41,42). Furnary *et al.* (40) showed that with improved glycemia (reducing glucose concentrations from 213 to 177 mg/dl), there is a reduction in mortality (from 5.3% to 2.5%), and that insulin infusion is independently protective against death. Similarly, Lazar *et al.* (41,42) showed that the maintenance of improved glycemia with insulin infusion leads to reductions in mortality, cardiac failure, and arrhythmias in patients undergoing CABG. A randomized trial by Quinn *et al.* (43) in patients without T2DM undergoing

Table 1 Major Trials of Insulin Therapy in ACS

Study (Year) (Ref. #)	N	Treatment	Mortality
GIK			
CREATE-ECLA (2005) (34)	20,201 STEMI (18% with T2DM)	IV GIK 24 h usual care vs. usual care	↑ 3% (p = NS)
OASIS-6 (2006) (35)	2,748 STEMI (15% with T2DM)	IV GIK 24 h vs. no infusion	↑ 14% 30 days (p = NS) ↑ 4% 6 months (p = NS)
OASIS-6/CREATE-ECLA pooled (2006) (34,35)	22,943 STEMI	IV GIK 24 h vs. usual care or no infusion	↑ 13% 3 days (p = 0.03) ↑ 4% 30 days (p = NS)
Insulin/glucose			
DIGAMI 1 (1995) (30)	620 ACS with diabetes	IV insulin/glucose ≥24 h, multidose SC insulin ≥3 months vs. standard care	↓ 18% inpatient (p = NS) ↓ 21% 90 days (p = NS) ↓ 29% 1 yr (p < 0.05) ↓ 28% 3.4 yrs (p = 0.011)
DIGAMI 2 (2005) (33)	1,235 ACS with T2DM	1: IV insulin/glucose ≥24 h, multidose SC insulin ≥3 months vs. 2: IV insulin/glucose ≥24 h, standard care vs. 3: standard care	↑ 3% 1 vs. 2 (p = NS) ↑ 23% 2 vs. 3 (p = NS)
Insulin/dextrose			
HI-5 (2006) (36)	240 STEMI with diabetes or admission glucose >140 mg/dl	IV insulin/dextrose ≥24 h vs. usual care	Intensive vs. usual care: 4.8% vs. 3.5% inpatient (p = NS) 7.1% vs. 4.4% 3 months (p = NS) 7.9% vs. 6.1% 6 months (p = NS)

ACS = acute coronary syndrome; CREATE-ECLA = Clinical Trial of Revascularization and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiológicas Latino America; DIGAMI = Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction; GIK = glucose-insulin-potassium; HI-5 = Hyperglycemia: Intensive Insulin Infusion In Infarction; IV = intravenous; NS = not significant; OASIS-6 = Organization for the Assessment of Strategies for Ischemic Syndromes; SC = subcutaneous; STEMI = ST-segment elevation myocardial infarction; T2DM = type 2 diabetes mellitus.

CABG with GIK therapy showed better myocardial function, decreased incidence of low cardiac output, and a reduction in myocardial injury.

Current Guidelines

While recognizing that the relationship between hyperglycemia and adverse ACS outcomes needs clarification, the American Heart Association Diabetes Committee, in a recent scientific statement, offered general recommendations for clinicians (44). During hospitalization, glucose levels should be measured in all patients with suspected or confirmed ACS as part of the initial laboratory evaluation (Level of Evidence: A). Glucose levels should be monitored closely in patients with ACS admitted to an ICU (Level of Evidence: B) and intensive glucose control considered when significant hyperglycemia (plasma glucose >180 mg/dl) is present (Level of Evidence: B); intravenous insulin is recommended for controlling glucose in ICU patients (Level of Evidence: B). In hospitalized patients with ACS and hyperglycemia but no prior diabetes history, the severity of their metabolic derangements should be evaluated (Level of Evidence: B). All patients with ACS and established diabetes, newly diagnosed diabetes, or evidence of insulin resistance should have an outpatient glucose control plan determined before discharge (Level of Evidence: C). Additional specific, evidence-based recommendations can be made as the gaps in the understanding of the hyperglycemia-ACS adverse outcomes relationship are addressed.

Conclusions

Hyperglycemia is associated with a graded increased risk of CV events. It is important for cardiology specialists to recognize that in patients with ACS, admission hypergly-

cemia has been linked both to increased early and to increased late mortality. Intensive glucose control in the hospital lowers the risk of mortality in critically ill patients. Clinical trials suggest that intensive glucose control lowers CV risk and clearly lowers the risk of renal disease. Standardized protocols are necessary that effectively achieve and maintain glucose levels within a given range and with minimal risk of hypoglycemia. Clear evidence to date shows that protocols using GIK therapy do not control glucose levels and do not lower mortality.

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