AHA Scientific Statement

Hyperglycemia and Acute Coronary Syndrome
A Scientific Statement From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism

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Abstract—Hyperglycemia is common and associated with markedly increased mortality rates in patients hospitalized with acute coronary syndromes (ACS). Despite the fact that several studies have documented this association, hyperglycemia remains underappreciated as a risk factor, and it is frequently untreated in ACS patients. This is in large part due to limitations of prior studies, and the remaining critical gaps in our understanding of the relationship between hyperglycemia and poor outcomes. The main objective of the present statement is to summarize the current state of knowledge regarding the association between elevated glucose and patient outcomes in ACS and to outline the most important knowledge gaps in this field. These gaps include the need to specifically define hyperglycemia, develop optimal ways of measuring and tracking glucose values during ACS hospitalization, and better understand the physiological mechanisms responsible for poor outcomes associated with hyperglycemia. The most important issue, however, is whether elevated glucose is a direct mediator of adverse outcomes in ACS patients or just a marker of greater disease severity. Given the marked increase in short- and long-term mortality associated with hyperglycemia, there is an urgent need for definitive large randomized trials to determine whether treatment strategies aimed at glucose control will improve patient outcomes and to define specific glucose treatment targets. Although firm guidelines will need to await completion of these clinical trials, the present statement also provides consensus recommendations for hyperglycemia management in patients with ACS on the basis of the available data. (***Circulation***. 2008;117:1610-1619.)

Key Words: AHA Scientific Statement ■ hyperglycemia ■ diabetes mellitus ■ acute coronary syndrome ■ prognosis

Hyperglycemia on admission in patients with acute coronary syndromes (ACS) is common, and it is a powerful predictor of survival and increased risk of in-hospital complications in patients both with and without diabetes mellitus. Despite the findings from prior studies, many gaps in knowledge currently exist in our understanding of the association between elevated glucose levels and adverse outcomes in patients with ACS. First, there is currently no consensus about the precise glucose value (or range of values) that should be considered abnormal on admission. Second, there is no consensus about the most suitable method to initially measure and subsequently monitor blood glucose levels in the acute setting of ACS.

Third, the benefits of treating hyperglycemia have not been established definitively, and the target value of blood glucose to be achieved with treatment remains undefined. Although several randomized trials have attempted to study the effects of glucose control with a variety of therapeutic approaches, because of their many limitations, the results have been mixed and at times confusing. Finally, the precise underlying pathophysiology of how hyperglycemia impacts clinical outcome in the setting of ACS is not well defined. Because of the importance of hyperglycemia in patients with ACS, this American Heart Association writing group has carefully reviewed the available data and prepared the following statement.

Figure 1. Mortality by admission glucose level.

Figure 2. Mortality by admission glucose level in patients with and without diabetes.

Relationship Between Admission Glucose Level and Outcomes in ACS Patients With and Without Preexisting Diabetes Mellitus

Numerous prior studies have established that hyperglycemia on admission is common in patients with ACS and is a risk factor for death and in-hospital complications.[1–25] Although the exact definition of hyperglycemia has not been established, the prevalence of admission hyperglycemia in prior epidemiological studies ranges from 25% to >50% of patients admitted with ACS.[1,3,14] In a meta-analysis of 15 relatively small and mostly older studies that evaluated the association between admission glucose level and death, Capes et al[3] demonstrated that the relative risk of in-hospital death in nondiabetic patients with acute myocardial infarction (AMI) with admission glucose ≥110 mg/dL was 3.9 compared with nondiabetic AMI patients who were normoglycemic. Among AMI patients with diabetes, those with admission glucose ≥180 mg/dL had a 70% relative increase in the risk of in-hospital death compared with diabetic patients with normal admission glucose values. Similarly, Foo et al[4] demonstrated a near-linear relationship between higher admission glucose levels and higher rates of left ventricular failure and cardiac death among 2127 patients with ACS. Meier et al[25] showed higher long-term mortality rates and larger infarct size (measured by creatine kinase and MB-fraction levels) among hyperglycemic AMI patients both with and without diabetes. Studies by Wahab et al[14] and Stranders et al[20] have also suggested that the admission hyperglycemia-associated risk is the highest in AMI patients without previously known diabetes.

The Cooperative Cardiovascular Project, the largest retrospective study of this subject to date, which examined the outcomes of 141 680 elderly AMI patients, demonstrated a significant 13% to 77% relative increase in 30-day mortality and a 7% to 46% relative increase in 1-year mortality depending on the degree of hyperglycemia (Figure 1).[1] This higher risk of both short- and long-term mortality persisted after controlling for higher burden of comorbidities (such as prior AMI and heart failure) and greater disease severity (higher Killip class, higher peak creatine kinase and creatinine levels, and lower ejection fraction) observed in patients with elevated glucose levels. Importantly, the glucose-associated risk of increased mortality was not restricted to patients with preexisting diabetes. As can be seen in Figure 2,
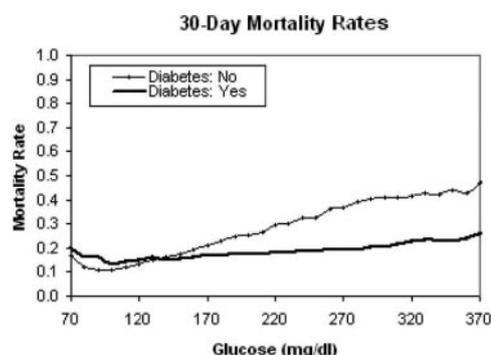
higher glucose levels were associated with a significantly greater increase in the risk of 30-day mortality in patients who did not have recognized diabetes than in those with established diabetes. In fact, in patients without known diabetes, the risk of 30-day mortality started to rise once admission glucose exceeded 110 mg/dL, whereas the threshold was higher among diabetic patients.

Data from several randomized clinical trials also confirm a powerful association between higher glucose levels and death in ACS populations. In the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation–Estudios Clínicos Latino America (CREATE-ECLA), which evaluated patients with ST-elevation AMI, the 30-day mortality rate was 6.6% among control group patients with baseline glucose in the lowest tertile, whereas those in the highest glucose tertile experienced a mortality rate of 14%.[26] In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study, the 6-month mortality rate was significantly higher among AMI patients with mean 24-hour glucose levels ≥144 mg/dL.[27]

Relationship Between Persistent Hyperglycemia During Hospitalization for ACS and Mortality

Most prior studies have focused predominantly on the prognostic value of admission glucose; however, admission glucose represents only a single measurement in time. Three prior studies suggest that hyperglycemia after hospital admission is more important prognostically than admission hyperglycemia alone. Suleiman and colleagues[24] have demonstrated in a sample of 735 nondiabetic AMI patients that the addition of a fasting glucose level within 24 hours of hospitalization to the admission glucose values improved the ability of the model to predict 30-day mortality rates. Svensson et al[22] showed that patients whose lowest blood glucose reading during hospitalization for ACS was >120 mg/dL had a 46% increase in relative risk of 30-day mortality compared with patients whose lowest values were between 56 and 119 mg/dL; this relationship was present regardless of admission glucose values. Goyal et al[28] evaluated the effect of the change between 24-hour and admission glucose levels and death and found that an increase in glucose values during the first 24 hours of hospitalization was associated with higher 30- and 180-day mortality rates, whereas a fall in the glucose

level was associated with improved survival; this relationship was present in patients without diabetes but not in those with diabetes. Importantly, this study was not able to differentiate between spontaneous and insulin-mediated decreases in glucose values.

These studies used glucose values that were based on a single measurement after hospital admission and thus were not indicative of overall hyperglycemia throughout the hospitalization. No prior study has used multiple glucose values obtained in a real-world clinical setting to define the prognostic value of persistently elevated glucose during the entire ACS hospitalization.

Physiological Link Between Elevated Glucose and Adverse Outcomes in Patients With ACS: Is Hyperglycemia a Marker of High Risk or a Mediator of Adverse Outcomes?

It is important to define the possible underlying pathophysiological mechanisms that might be responsible for the adverse prognostic impact of hyperglycemia in the setting of ACS. Multiple physiological studies demonstrate that hyperglycemia may have a direct detrimental effect on ischemic myocardium through a variety of mechanisms. Kersten and colleagues[29,30] have shown decreased collateral circulation and increased infarct size in the setting of severe hyperglycemia. Studies in animals have shown that acute hyperglycemia abolishes ischemic preconditioning and promotes apoptosis.[30,31] Hyperglycemia is also associated with elevated systolic and diastolic blood pressures and QT prolongation, changes that were alleviated with hyperglycemia correction.[32] Marfella et al[33] have reported similar hemodynamic and electrocardiogram changes, as well as elevated catecholamine levels, in healthy human volunteers with artificially induced hyperglycemia (glucose >270 mg/dL).

In diabetic patients, postprandial hyperglycemia is associated with development of myocardial perfusion defects due to microvascular dysfunction, a condition that improves with better glucose control.[34,35] Hyperglycemic patients with ST-elevation AMI have lower rates of spontaneous reperfusion.[36] Microvascular dysfunction was also demonstrated in hyperglycemic patients with AMI undergoing reperfusion. Specifically, Iwakura et al[5] showed a higher incidence of the no reflow phenomenon by myocardial contrast echocardiography in patients with elevated glucose levels after successful reperfusion. Human studies have also linked elevated glucose levels with endothelial dysfunction, as measured by endothelium-mediated brachial artery vasodilation,[37] in which the level of endothelial dysfunction was correlated with the level of hyperglycemia.

Several studies have shown that hyperglycemia is associated with a prothrombotic state. Acutely hyperglycemic rats exhibit lower tissue plasminogen activator activity and higher plasminogen activator inhibitor levels.[38] Hyperglycemic but not euglycemic clamp conditions in patients with type 2 diabetes mellitus were found to be associated with increased platelet aggregation and higher thromboxane A2 and von Willebrand factor activity.[39] Acute hyperglycemia induces a shortening of the half-life of fibrinogen and platelet aggregation and results in increased levels of fibrinopeptide A,
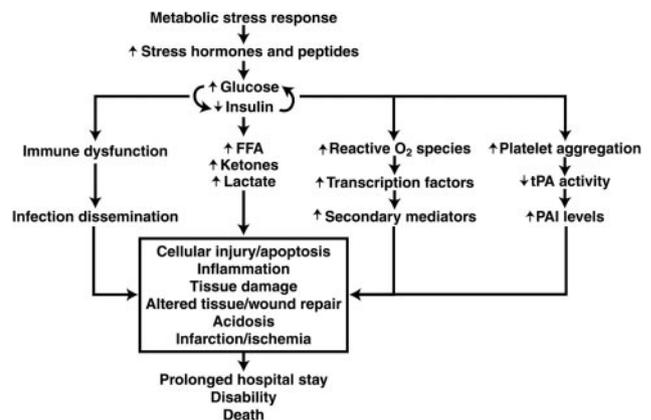

Figure 3. Detrimental physiological impact of hyperglycemia. Modified from Clement et al.[57] FFA indicates free fatty acids; tPA, tissue plasminogen activator; and PAI, plasminogen activator inhibitor.

prothrombin fragments, and factor VII, all phenomena that suggest increased activation of prothrombotic factors.[40–44]

Higher glucose levels have also been shown to be associated with increased markers of vascular inflammation. Both in vitro and in vivo studies have linked hyperglycemia with elevated levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α.[45,46] Tumor necrosis factor-α has been shown to extend infarct size in laboratory animals and to induce myocardiocyte apoptosis.[47,48] In vitro and in vivo studies also demonstrated induction of the proinflammatory transcription factor nuclear factor-κB in a setting of elevated glucose.[49,50] Glucose ingestion in healthy human volunteers is also associated with increased production of other proinflammatory factors, such as activator protein 1 and early growth response 1, and increased expression of the genes regulated by them, including the genes for matrix metalloproteinases-2 (*MMP-2*) and -9 (*MMP-9*) and tissue factor (*TF*).[51] Hyperglycemia has also been shown to be associated with increased generation of reactive oxygen species, which can induce tissue injury.[52,53] Interestingly, recent data from human studies suggest that acute fluctuations in glucose levels may have an even more powerful impact on oxidative stress than chronic, sustained hyperglycemia.[54]

Higher glucose levels in patients with ACS have also been associated with higher free fatty acid concentrations, insulin resistance, and impaired myocardial glucose utilization, thus increasing the consumption of oxygen and potentially worsening ischemia.[55,56] Higher free fatty acid concentrations have been linked to increased incidence of malignant ventricular arrhythmias.[55,56] Finally, hyperglycemia has been linked to an impaired immune response.[57] Figure 3 summarizes the detrimental effects of glucose on cardiovascular and other organ systems.

Given the multiple detrimental effects of elevated levels of glucose on the cardiovascular system, it is possible that poor glucose control during hospitalization may have a direct effect on outcomes in patients hospitalized with ACS. As demonstrated by several investigators, insulin-mediated normoglycemia may attenuate some of the detrimental effects of elevated glucose; specifically, it may have antiinflammatory effects (such as reducing C-reactive protein levels) in both

AMI and post-coronary artery bypass grafting patients.[58–61] Insulin may also inhibit generation of reactive oxygen species, may have profibrinolytic and antiapoptotic effects,[58,62–65] and may improve myocardial blood flow.[66] Whether the possible beneficial effects of glucose control in the setting of ACS could be attributed primarily to glucose normalization, insulin administration, or both remains debatable; however, the preponderance of evidence suggests that insulin therapy alone, without achievement of normoglycemia, does not improve outcomes. Whether insulin-mediated normoglycemia will improve survival and reduce complications in patients with ACS remains to be established.

The differential impact of hyperglycemia on outcomes in patients with and without known diabetes has been a consistent finding by several investigators. Specifically, elevated glucose appears to be a much stronger predictor of adverse events in patients without previously recognized diabetes than in those with established diabetes. Although the specific pathophysiological mechanisms behind this phenomenon are not well understood, several potential explanations exist. Some hyperglycemic patients without known diabetes (particularly those with severe hyperglycemia) likely have diabetes that was neither appropriately recognized nor treated before hospitalization; these patients may, therefore, represent a higher-risk cohort. Furthermore, hyperglycemic AMI patients without known diabetes are much less likely to be treated with insulin than those with diabetes, even when glucose levels are markedly elevated. Given the possible beneficial effects of insulin in a setting of myocardial ischemia, this therapeutic difference may account in part for the disparity in outcomes. Finally, it is also possible that a higher degree of stress (or severity of illness) is required to produce a similar degree of hyperglycemia in patients without known diabetes than in those with diabetes. A better understanding of this important interaction between hyperglycemia, the presence of diabetes, and adverse outcomes is needed and should be the subject of further research.

Metrics of Glucose Control During Hospitalization and Their Prognostic Association With Outcomes in ACS

Although hemoglobin A_{1c} (HbA_{1c}) is a useful tool in assessing average glucose control in the outpatient setting, it has limited prognostic value in predicting in-hospital and short-term mortality rates in ACS patients.[19,67] In the inpatient setting, where the duration of care is relatively brief, there is no single laboratory test (such as HbA_{1c}) that can accurately assess the degree of glucose control during the entire hospitalization or part of the hospitalization. Instead, multiple glucose results must be analyzed; these results may be obtained either from plasma samples or from capillary blood ("finger sticks") and represent a variety of fasting and nutritional conditions. The development of a summary measure of average glucose control from multiple inpatient glucose measurements is likely to be of critical importance if the nature of the relationship between glucose control and death in ACS is to be determined accurately. Several candidates for this measurement exist, such as mean glucose level,[68,69] time-averaged glucose level, hyperglycemia index,[70] and patient-day glucose level.[71] No prior studies have systematically evaluated the prognostic association of these metrics with outcomes in ACS.

Another dimension of measuring glucose in the inpatient setting deserves brief mention. Some prior epidemiological studies and randomized clinical trials have used plasma glucose, whereas others used whole-blood glucose measurements. These are not identical; in fact, plasma glucose is $\approx$10% higher than whole-blood glucose. Care should be taken to account for this difference when the results of prior studies are interpreted and applied in clinical care.

New technologies, such as continuous glucose monitors, are currently emerging that may simplify the task of multiple glucose measurements in the inpatient setting; however, there are currently no data on the use of these technologies in patients hospitalized with ACS. Whether these devices will have a role in future management of hyperglycemic ACS is therefore unclear.

Relationship Between Intensive Insulin Therapy, Glucose Control, and Outcomes in Hyperglycemic Patients With ACS and in Other Critically Ill Patient Populations

Prior randomized clinical trials of glucose control in ACS have been limited primarily to patients with known diabetes, and their results have been inconsistent (Table). The 2 most relevant studies for glycemic control in ACS patients are the DIGAMI (Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction) studies. The original DIGAMI study from 1995 studied the effects of intensive in-hospital insulin treatment (insulin-glucose infusion for at least 24 hours followed by multidose subcutaneous insulin regimen) versus usual care in 620 AMI patients with established diabetes and/or admission glucose of >11 mmol/L (200 mg/dL).[72] Better glucose control was achieved in the arm receiving more intensive insulin therapy (mean 24-hour posttreatment glucose of 173 mg/dL versus 210 mg/dL in the control group). A significant mortality benefit was seen in the intervention arm at both the 1- and 3.4-year follow-up points.[73] The original DIGAMI study was the only randomized trial of glucose control in AMI to date to have achieved a significantly lower glucose level in the intervention arm compared with the control arm; it also happens to be the only randomized trial to have demonstrated a survival benefit associated with better glucose control.

The DIGAMI-2 trial[74] attempted to study 3 alternative treatment regimens: acute insulin-glucose infusion followed by insulin-based long-term glucose control; insulin-glucose infusion followed by standard glucose control on discharge; and routine metabolic management in both inpatient and outpatient settings. Although there were no differences in outcomes among the 1253 randomized AMI patients, this may be attributable to the similar short-term glucose control and identical longer-term glucose control obtained among the 3 groups. Most importantly, the longer-term fasting glucose target of 90 to 126 mg/dL was never achieved in the intensive-treatment group. Thus, despite its intent, DIGAMI-2 ended up comparing different insulin-treatment strategies, not different intensities of glucose control. Further-

Table. **Summary of Clinical Trials in ACS Patients With Hyperglycemia**

Study	Sample Size, n	Patient Population	Intervention	Glucose Targets	Glucose Contrast Between Groups	Outcomes
DIGAMI	620	AMI with either diabetes or admission glucose >200 mg/dL	Glucose-insulin infusion for at least 24 h, then multidose subcutaneous insulin for ≥3 mo vs conventional care	126–196 mg/dL	Mean 24-h glucose was significantly lower in the intervention arm than in the control arm (173 vs 210 mg/dL, respectively)	19% Mortality in intervention arm vs 26% in control arm (P=0.011) at 1 y
DIGAMI-2	1253	AMI with either diabetes or admission glucose >200 mg/dL	Group 1: Glucose-insulin infusion for at least 24 h, then multidose subcutaneous insulin for ≥3 mo. Group 2: Glucose-insulin infusion for at least 24 h, then conventional care. Group 3: Conventional care.	126–180 mg/dL in-hospital for groups 1 and 2. Long-term target for group 1 was 90–126 mg/dL fasting glucose.	Overall, no significant difference in glucose control between the 3 groups. Long-term fasting glucose target was not achieved in group 1.	No difference in mortality at 2 years between the 3 groups
HI-5	244	AMI with either diabetes or admission glucose >140 mg/dL	Dextrose-insulin infusion for at least 24 h vs conventional care	72–180 mg/dL	No significant difference in mean 24-h glucose between groups	No difference in mortality (in-hospital, 3 and 6 mo) between intervention and control groups. Intervention group had lower rate of post-MI heart failure (12.7% vs 22.8%, P=0.04) and reinfarction (2.4% vs 6.1%, P=0.05)
CREATE-ECLA	20 201	STEMI; no requirement for diabetes or hyperglycemia on admission	GIK infusion for 24 h vs conventional care	None	Mean 24-h glucose 155 mg/dL in GIK group vs 135 mg/dL in control group	No difference in 30-d mortality between intervention and control arms

MI indicates myocardial infarction; STEMI, ST-segment–elevation myocardial infarction.

more, like the original DIGAMI trial, DIGAMI-2 did not include any hyperglycemic patients without previously known diabetes, the group with the highest risk of glucose-associated death.

The HI-5 study attempted to rectify some of the issues that were encountered in DIGAMI-2.[27] It was the first randomized clinical trial of intensive insulin infusion that included hyperglycemic AMI patients without previously established diabetes. Patients assigned to the intensive insulin-infusion arm received standard insulin and dextrose infusion that was then adjusted to maintain glucose levels between 72 and 180 mg/dL. Patients in the conventional arm received their baseline diabetes medications (including subcutaneous insulin; additional short-acting subcutaneous insulin was permitted for those with a glucose level >288 mg/dL. There were only 244 patients randomized in the study. There was no difference in mortality rates among the groups during hospitalization or at 3 or 6 months. There were, however, statistically and clinically significant reductions in post–myocardial infarction heart failure during hospitalization (10% absolute risk reduction) and in reinfarction at 3 months (3.7% absolute risk reduction).

There are several very important issues that need to be considered in the interpretation of this study. First and most importantly, the HI-5 study suffered from the same issues that complicated the DIGAMI-2 trial. Specifically, the mean 24-hour glucose values were similar in the intensive-treatment arm (141 mg/dL) and the conservative-treatment arm (153 mg/dL, P=NS). Thus, as with the DIGAMI-2 study, the HI-5 investigators ended up comparing 2 different insulin strategies but not 2 different intensities of glucose control. In addition, no provisions for tight glucose control were made after the initial 24 hours of hospitalization, and the study never recruited the intended number of patients (244 patients recruited instead of the 850 patients planned for on the basis of the power calculations).

CREATE-ECLA, a multinational, randomized clinical trial, compared the impact of glucose-insulin-potassium (GIK) infusion and placebo on mortality in 20 201 AMI patients.[26] From the outset, CREATE-ECLA was not designed to be a study of intensive glucose control in AMI. There was no requirement for admission hyperglycemia for study entry, and patients with both normal and elevated glucose levels on admission were included. Unlike

DIGAMI-1 and -2, glucose control was not the primary intervention target. There were also no prespecified targets for glucose control with GIK infusion, and in fact, posttreatment glucose levels (24 hours after randomization) were higher in the GIK group (155 mg/dL) than in controls (135 mg/dL). There were no differences in rates of 30-day mortality, cardiac arrest, cardiogenic shock, or reinfarction between the GIK and placebo groups.

However, studies in other critically ill patient populations show that successful strict glucose control, regardless of diabetes status, may result in better outcomes. Specifically, a landmark study by van den Berghe and colleagues[75] has demonstrated that target-driven glucose control with intensive insulin therapy (goal of whole-blood glucose level of 80 to 110 mg/dL) reduced intensive care unit (ICU) mortality rates from 8.0% to 4.6% in surgical patients and in-hospital mortality rates from 10.9% to 7.2%. This improvement was entirely attributable to the decrease in the mortality rate seen in patients who remained in the ICU for >5 days. The relative risks of ICU complications, such as renal failure, septicemia, and transfusion requirements, were also markedly reduced by 41% to 50%. Importantly, the benefit was achieved with few adverse events (such as hypoglycemia). The findings from this study clearly suggest that control of hyperglycemia may be more critical than the dose of insulin administered. In a recent follow-up study by the same group, which involved medical ICU patients, intensive glucose control reduced morbidity but not mortality in the intention-to-treat analysis; however, the mortality rate was lower in the intervention arm among those patients who required ICU care for ≥3 days.[76] Analysis of pooled data from both surgical and medical ICU studies by van den Berghe and colleagues[77] demonstrated that intensive glucose control in the intention-to-treat analysis was associated with significant reductions in mortality (24% relative risk reduction) and morbidity (42% relative risk reduction in kidney injury); patients who achieved mean whole-blood glucose levels <110 mg/dL had the lowest mortality and complication rates but also had the highest rate of hypoglycemia (10.7%). The mortality and morbidity benefit of intensive glucose control, once again, was not seen in the subgroup of patients who stayed in the ICU <3 days. Interestingly, the benefit of intensive glucose control was also not observed among patients with established diabetes, which again suggests that the relationship between glucose control and outcomes may be very different in patients with and without preexisting diabetes.

Because of significant differences in patient populations, the results of these studies by van den Berghe et al can not simply be extrapolated to patients with ACS, particularly because many patients with ACS have ICU stays shorter than 3 days. Whether strict glucose control in hyperglycemic patients with ACS will result in similar reductions in mortality and in-hospital complications remains to be established and needs to be investigated in well-designed randomized clinical trials.

Current Patterns of Glucose Management During ACS Hospitalization

A paucity of data exists regarding current patterns of glucose management across hospitals. Prior studies have shown that even among patients with severe hyperglycemia on admission (glucose >240 mg/dL), 78% of patients without known diabetes and 27% of patients with diabetes do not receive any insulin.[1] However, an important limitation of these prior studies was their inability to determine how many patients with elevated glucose on admission also had persistent hyperglycemia during hospitalization. It is possible that some AMI patients were not treated with insulin because their hyperglycemia resolved. Because of this limitation, it is still unknown how many patients with persistent hyperglycemia during hospitalization receive insulin therapy and how many receive intensive therapy. Addressing these knowledge gaps would help determine whether significant variations in regard to glucose control exist among hospitals and whether these variations are associated with different outcomes in patients hospitalized with ACS.

Prognostic Value of Hypoglycemia

Another important aspect of glucose control in ACS that deserves mention is the adverse impact of hypoglycemia on outcomes in patients with ACS. Most of the existing data on this issue come from prior epidemiological studies. Specifically, in the study by Svensson et al,[22] a single blood glucose measurement of <54 mg/dL during hospitalization was associated with a 93% increase in relative risk of long-term mortality. Other studies also demonstrated that hypoglycemia on admission is associated with increased risk of death or MI at 30 days.[78] Whether this adverse prognostic impact extends to all hypoglycemic events versus only symptomatic/clinically important hypoglycemic episodes is not currently known.

Executive Summary

Elevated glucose is common in ACS patients and is a powerful predictor of adverse outcomes.[1–25] Yet, despite a growing body of knowledge about the prognostic importance of elevated glucose in ACS patients and some evidence of improved outcomes from tight glucose control in other critically ill populations, clinicians currently have limited guidance regarding the evaluation and management of hyperglycemia in the ACS setting.

The lack of specific direction in regard to glucose management in ACS patients stems from methodological limitations of prior studies and the lack of convincing data from randomized trials to establish the benefit of tight glucose control in this patient population. Because of these limitations, multiple critical knowledge gaps currently exist in our understanding of the relationship between elevated glucose and adverse outcomes in ACS patients.

Areas in Need of Further Investigation

It is recommended that the following specific areas be addressed by future research:

1. Establish whether persistent hyperglycemia during ACS hospitalization has greater impact on prognosis than

admission hyperglycemia alone, and develop the optimal way to assess overall glucose control during ACS hospitalization.

2. Determine whether there is a critical period of vulnerability from hyperglycemia in ACS patients (ie, whether hyperglycemia-associated risk is time dependent).

3. Define target glucose levels that are associated with the best outcomes in hospitalized ACS patients, and determine whether these targets differ in patients with and without preexisting diabetes mellitus.

4. Establish what clinical benefits, if any, may be realized from achieving the specified targets with intensive glucose control and whether these benefits extend to patients both with and without preexisting diabetes. These benefits may include improved survival, shorter ICU and hospital length of stay, lower rate of in-hospital complications, and better left ventricular systolic function, among others. In addition, specific aspects of intensive glucose control associated with improved outcomes should also be defined. These aspects may include:

   a. Posttreatment glucose levels achieved
   b. Absolute change in glucose levels with treatment
   c. Timing of therapy

5. Describe current patterns of glucose control and management among patients hospitalized with ACS.

6. Demonstrate the safety, feasibility, and effectiveness of intensive glucose control protocols in ACS patients.

7. Identify mechanisms responsible for poor short- and long-term prognosis in hyperglycemic ACS patients without previously recognized diabetes. An understanding of these mechanisms would inform the development of specific interventions to improve outcomes in this patient group that can later be tested in randomized clinical trials.

Although many of these questions can be answered by observational studies, randomized multicenter clinical trials will be needed to definitively establish whether intensive glucose control will reduce the associated increased mortality rate and higher rates of complications in hospitalized ACS patients with hyperglycemia. Ideally, these trials should:

1. Include hyperglycemic patients both with and without prior diabetes (suggested definition of hyperglycemia is admission plasma glucose >140 mg/dL);

2. Use glucose control protocols with established effectiveness and safety, with the goal of achieving euglycemia in the intervention arm while avoiding hypoglycemia; and

3. Afford sufficient statistical power to assess mortality as a primary outcome.

Recommendations

Until the above-mentioned knowledge gaps have been addressed appropriately, specific, evidence-based recommendations will be difficult to make with regard to the diagnosis and management of hyperglycemia during ACS hospitalization. The following set of recommendations should therefore be viewed by clinicians only as a general reference. There is currently insufficient evidence to consider glucose control as a quality measure during ACS hospitalization, although this position may change in the future.

1. Glucose level should be a part of the initial laboratory evaluation in all patients with suspected or confirmed ACS. (*Level of Evidence A*)

2. In patients admitted to an ICU with ACS, glucose levels should be monitored closely (*Level of Evidence B*). It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (plasma glucose >180 mg/dL), regardless of prior diabetes history (*Level of Evidence B*). Although efforts to optimize glucose control may also be considered in patients with milder degrees of hyperglycemia (*Level of Evidence C*), the data regarding a benefit from this approach are not yet definitive, and future randomized clinical trials in ACS populations will be needed to determine whether it improves patient outcomes. The precise goal of treatment has not yet been defined. Until further data are available, approximation of normoglycemia appears to be a reasonable goal (suggested range for plasma glucose 90 to 140 mg/dL), as long as hypoglycemia is avoided. (*Level of Evidence C*)

3. Insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among patients hospitalized in the ICU. Effective protocols for insulin infusion and glucose monitoring have been developed in other patient populations.[79,80] Care should be taken to avoid hypoglycemia, which has been shown to have an adverse prognostic impact.[22] (*Level of Evidence B*)

4. Treatment should be instituted as soon as feasible, without compromising the administration of life-saving and evidence-based treatments. (*Level of Evidence C*)

5. In patients hospitalized in the non-ICU setting, efforts should be directed at maintaining plasma glucose levels <180 mg/dL with subcutaneous insulin regimens. (*Level of Evidence C*)

6. ACS patients with hyperglycemia but without prior history of diabetes should have further evaluation (preferably before hospital discharge) to determine the severity of their metabolic derangements. This evaluation may include fasting glucose and HbA$_{1C}$ assessment and, in some cases, a postdischarge oral glucose tolerance test. (*Level of Evidence B*)

7. Before discharge, plans for optimal outpatient glucose control should be determined in those patients with established diabetes, newly diagnosed diabetes, or evidence of insulin resistance. (*Level of Evidence C*)

Summary

Hyperglycemia is common, frequently untreated, and strongly associated with adverse outcomes in patients hospitalized with ACS. Multiple gaps still exist in our understanding of the relationship between elevated glucose and adverse outcomes, most importantly, whether hyperglycemia is a marker or a mediator of higher mortality and whether treatment of hyperglycemia improves outcomes. Addressing these knowledge gaps in future studies may provide an opportunity to improve care and outcomes in patients with ACS.

Disclosures

Writing Group Disclosures

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*Modest.

Reviewer Disclosures

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Hyperglycemia and Acute Coronary Syndrome: A Scientific Statement From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism

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Correction

In the article by Deedwania et al, "Hyperglycemia and Acute Coronary Syndrome: A Scientific Statement From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism" which published ahead of print on February 25, 2008, and appeared in the March 25, 2008, issue of the journal (*Circulation.* 2008;117;1610–1619), several corrections were needed.

On page 1617, in the Writing Group Disclosures table, Dr Mazzone's disclosures were incorrect at the time of publication. Research Grant was listed as "None" and has been updated to read, "Novartis; Takeda." Other Research Support was listed as "Takeda*; Novartis*" and has been updated to read, "None." Speakers' Bureau/Honoraria was listed as "Merck" and has been updated to read, "Amylin; Merck; Takeda." Ownership Interest was listed as "Takeda*; Novartis*; Merck"; Sanofi-Aventis*; GlaxoSmithKline*" and has been updated to read, "None." Consultant/Advisory Board was listed as "None" and has been updated to read, "Amylin; Merck; Takeda." Other was listed as "Pfizer*; GlaxoSmithKline*; Takeda*" and has been updated to read, "None."

These corrections have been made to the current online version of the article, which is available at http://circ.ahajournals.org/cgi/content/full/117/12/1610.