Diabetes and Cardiovascular Disease

Glucose-Lowering Targets for Patients With Cardiovascular Disease

Focus on Inpatient Management of Patients With Acute Coronary Syndromes

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The observation that elevated glucose levels can occur in patients hospitalized with acute coronary syndromes (ACS) was made many decades ago. Since then, a multitude of studies have documented that hyperglycemia is common, affects patients with and without established diabetes mellitus, and is associated with adverse outcomes, with a graded increase in the risk of mortality and complications across the spectrum of glucose elevations observed. However, a number of critical gaps in knowledge remain. These include, first and foremost, a better understanding of whether glucose level is simply a risk marker of greater illness severity or a risk factor with a direct causal relationship to the observed adverse outcomes in patients with ACS. Similarly, it remains unclear whether interventions to lower glucose in patients with ACS (unstable angina, non–ST-segment elevation myocardial infarction [MI], and ST-segment elevation MI) can improve survival and other outcomes and, if so, what the optimal targets, therapeutic strategies, and timing for such interventions should be during ACS.

In this article, we will review current knowledge about the association between glucose levels and outcomes of patients hospitalized with ACS; describe the available data with regard to inpatient glucose management in patients with ACS, as well as comparative data across the clinical spectrum of critically ill hospitalized patients; address the controversies in this field; and offer practical recommendations for patient management based on the existing data.

Definition of Hyperglycemia in Patients With ACS

Although hyperglycemia occurs commonly in hospitalized patients with cardiovascular disease conditions other than ACS, the relationship between glucose levels and outcomes has not been well studied among those patient populations. Therefore, the emphasis of this review will be on the care of patients with ACS.

There is currently no uniform definition of hyperglycemia in the setting of ACS. Prior studies used various hyperglycemia cut points, ranging from ≥110 to ≥200 mg/dL. This is compounded by different timing of glucose level assessments in this context. Most prior studies defined hyperglycemia on the basis of the first available (or “on-arrival”) glucose value, whereas others used fasting glucose and glucose values averaged over a period of time, such as the first 24 hours or the entire duration of hospitalization. Recently, a random glucose level >140 mg/dL observed at any point over the course of ACS hospitalization has been suggested as the definition of hyperglycemia in the American Heart Association Scientific Statement on Hyperglycemia and Acute Coronary Syndrome. This recommendation is based, in part, on epidemiological studies demonstrating that admission, mean 24-hour, and mean hospitalization glucose levels above 120 to 140 mg/dL are associated with increased short-term mortality risk and that decline in glucose levels below 140 mg/dL during ACS hospitalization is associated with better survival, although no cause-and-effect conclusions can be drawn from these data because of their observational nature.

However, the nature of the relationship between glucose levels and short-term mortality differs in patients with and without diabetes mellitus, with a paradoxically greater magnitude of association in those without versus those with prevalent diabetes mellitus. The risk of mortality gradually rises when glucose levels exceed 110 to 120 mg/dL in patients without diabetes mellitus, whereas in patients with established diabetes mellitus, this risk does not increase substantially until glucose levels exceed 200 mg/dL. Thus, different thresholds may be appropriate to define hyperglycemia depending on the presence or absence of known diabetes mellitus.

Prevalence of Elevated Glucose Levels in ACS

Numerous studies have documented that elevated glucose occurs commonly in patients hospitalized with ACS. Although the definition of hyperglycemia varies across studies, the largest investigations show that the overall prevalence of elevated glucose levels (≥140 mg/dL) at the time of hospital admission varies between 51% and 58%. Importantly, >50% of patients with ACS who are hyperglycemic on hospital arrival do not have known diabetes mellitus.

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Although glucose levels normalize in some ACS patients after admission (either spontaneously or because of targeted pharmacological interventions), the prevalence of persistent hyperglycemia remains >40% throughout the course of hospitalization, and the prevalence of severe, sustained hyperglycemia (average hospitalization glucose >200 mg/dL) is ≈14%. Although persistent hyperglycemia occurs more commonly in patients with established diabetes mellitus (78%) than in those without diabetes mellitus (26%), >40% of patients with persistent hyperglycemia do not have known diabetes mellitus.

### Relationship Between Glucose Levels and Mortality in ACS

Multiple studies have now proven a powerful, independent relationship between elevated glucose and increased risk of mortality and other adverse clinical outcomes in patients hospitalized with ACS. Plausible pathophysiological underpinnings potentially contributing to these observed associations derive from a plethora of ex vivo animal and human studies, which show that hyperglycemia may mediate adverse effects on inflammation, cell injury, apoptosis, ischemic myocardial metabolism, endothelial function, the coagulation cascade, and platelet aggregation in the setting of acute ischemia. The association between higher glucose and greater mortality risk has been established across various glucose metrics and across the spectrum of ACS and applies to both short- and longer-term outcomes.

The association between hyperglycemia and adverse outcomes among patients with ACS has been quantitatively summarized on the basis of data from a large series of relatively small human studies collected over a period of 3 decades by Capes et al. This systematic overview demonstrated that among ACS patients without known diabetes mellitus, the relative risk of in-hospital mortality was 3.9 times higher in those with initial glucose of ≥110 mg/dL compared with normoglycemic patients (95% confidence interval, 2.9 to 5.4). Among ACS patients with established diabetes mellitus, those with initial glucose ≥180 mg/dL had a 70% increase in the relative risk of in-hospital mortality compared with normoglycemic patients. More recent studies confirmed these findings and extended them across the broader range of ACS to include ST-segment elevation MI, non–ST-segment elevation MI, and unstable angina, demonstrating a significant increase in the risk of short- and long-term mortality, as well as incident heart failure, in hyperglycemic ACS patients both with and without diabetes mellitus. The largest observational study to date to address this issue used the data from the Cooperative Cardiovascular Project and showed a near-linear relationship between higher admission glucose level and greater risk of mortality at 30 days and at 1 year in >140,000 patients hospitalized with acute MI (AMI). A similar relationship between elevated glucose and increased risk of death was also shown with other glucose metrics, such as postadmission fasting glucose, and with outcomes other than mortality, including such intermediates associated with adverse clinical outcomes as “no-reflow phenomenon” after percutaneous coronary intervention; greater infarct size; worse left ventricular systolic function; and acute kidney injury.

The association between hyperglycemia and increased risk of death is not limited to the initial stages of ACS hospitalization. To the contrary, in a study of nearly 17,000 patients hospitalized with AMI across 40 US hospitals, persistently elevated glucose during hospitalization was a much better discriminator of adverse events than was hyperglycemia on admission (C statistic, 0.70 versus 0.62; P < 0.0001). There was a significant, gradual increase in the risk of in-hospital mortality with rising mean hospitalization glucose levels (Figure 1). Observational subanalyses of data from randomized clinical trials of glucose-insulin-potassium (GIK) therapy and of targeted glucose control in ACS also confirm the relationship between persistent hyperglycemia and increased mortality risk.

Another important observation is that the nature of the relationship between higher glucose levels and increased mortality is different in patients with and without established diabetes mellitus. Regardless of the glucose metrics used, the mortality risk starts rising at considerably lower glucose levels and increases at a much steeper slope in patients without known diabetes mellitus compared with those who have previously diagnosed diabetes mellitus (Figure 1). This phenomenon is incompletely understood, and several possible explanations have been proposed. Many patients presenting with hyperglycemia in the absence of previously diagnosed diabetes mellitus actually have diabetes mellitus that simply has not been recognized or treated before hospitalization, representing a higher-risk cohort because other undiagnosed and untreated cardiovascular risk factors may be more prevalent in this group of patients. Moreover, although the effect of targeted glucose control and insulin therapy in this clinical setting remains uncertain, nondiabetic ACS patients with hyperglycemia are less likely to be treated with insulin than those with established diabetes mellitus, even when glucose levels are markedly elevated. Further contributing to this consistent observation is the fact that patients with established diabetes mellitus tend to have clustering of numerous risk factors contributing to clinical risk, which may attenuate the magnitude of risk independently associated with any
single factor, such as hyperglycemia. Finally, it is possible that higher degrees of stress and illness severity are required to produce similar degrees of hyperglycemia in patients without known diabetes mellitus compared with those with established diabetes mellitus.

**Dynamic Changes in Glucose Levels During ACS and Mortality**

Adding to the growing body of data on the relationship between hyperglycemia and adverse events in hospitalized ACS patients, several studies have shown that dynamic changes in glucose values are also strongly associated with patient survival. In post hoc analyses of data from the Complement And ReDuction of INfarc size after Angioplasty or Lytics (CARDINAL) trial, a randomized clinical trial that investigated the effect of a complement inhibitor, pexelizumab, in 1903 patients with ST-segment elevation MI, a decline in glucose of ≥30 mg/dL during the first 24 hours of hospitalization was associated with lower risk of 30-day mortality compared with the groups who had either no change or an increase in glucose values. Similarly, in a study of nearly 8000 patients hospitalized with ACS in the United States who had hyperglycemia on arrival, glucose normalization after admission was associated with better patient survival, even after adjustment for confounders (Figure 2). Another study has shown that glucose normalization took place after insulin administration in some patients, many patients experienced normalization of their glucose values spontaneously (without any glucose-lowering interventions). Interestingly, improved survival was observed regardless of whether glucose normalization occurred as the result of insulin therapy or happened spontaneously. In fact, glucose normalization, and not insulin therapy per se, was associated with better outcomes.

**Clinical Trials of Glucose Control in Patients With ACS**

Although the strong relationship between elevated glucose levels and greater risk of death in ACS is incontrovertible, a critical question remains unanswered: Is hyperglycemia a direct mediator of increased mortality and complications in patients with ACS, or is it simply a marker of greater disease severity and comorbidity? To definitively answer this question, large randomized clinical trials of target-driven intensive glucose control in hospitalized ACS patients are required. Because no such clinical outcomes trial has been performed to date, this issue continues to be highly controversial and cannot be presently addressed with certainty. Nevertheless, some insights may be gained from critical appraisal of a series of small clinical trials of targeted glucose control in the ACS setting, trials of GIK therapy that used a hyperinsulinemic, hyperglycemic infusion strategy, and data from studies of targeted glucose control conducted in non-ACS clinical settings.

Because of marked variability in the insulin-infusion strategies used and the hypotheses tested across the clinical trials executed to date, one must first establish several key parameters to appropriately identify those randomized studies that provide useful information with regard to the effect of targeted glucose control in the ACS setting. These parameters include the following: (1) the presence of hyperglycemia at the time of patient randomization, with or without an antecedent diabetes mellitus diagnosis (because targeted glucose management is unlikely to yield benefit in the absence of hyperglycemia); (2) target-driven glucose control as the primary tested intervention, with substantially lower glucose targets in the intervention versus control arm; (3) the achievement of a clinically and statistically significant difference in glucose values between intervention and control groups after randomization; and (4) the assessment of treatment effects on meaningful patient outcomes as opposed to intermediate end points.

To date, no ACS trial has fulfilled all of these criteria with any degree of rigor. A few studies fulfilling some but not all of these criteria are summarized in the Table. The trial most closely satisfying the listed parameters is the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, with a number of key caveats in regard to its interpretation. Another study has shown that glucose control in hospitalized ACS patients are required. Because no such clinical outcomes trial has been performed to date, this issue continues to be highly controversial and cannot be presently addressed with certainty. Nevertheless, some insights may be gained from critical appraisal of a series of small clinical trials of targeted glucose control in the ACS setting, trials of GIK therapy that used a hyperinsulinemic, hyperglycemic infusion strategy, and data from studies of targeted glucose control conducted in non-ACS clinical settings.

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arm (173 versus 211 mg/dL; \( P<0.0001 \)), although average glucose values remained significantly elevated in both groups; the differences between the groups were smaller by hospital discharge but remained statistically significant (148 versus 162 mg/dL; \( P<0.01 \)). Despite this early contrast in glucose levels between the groups, no significant differences in fasting glucose values were observed at any subsequent time point throughout the follow-up extending over 12 months from enrollment; however, HbA1C levels were significantly lower in the intervention versus control group at 3 months (7.0% versus 7.5%; \( P<0.01 \)). Also of note, hypoglycemia (not explicitly defined in the initial study reports) was observed in 15% of the insulin infusion patients compared with none in the usual care group, and this resulted in discontinuation of the protocol treatment in 10% of participants. For the primary end point of all-cause mortality at 3 months, there was no significant difference between the randomized groups (38 versus 49 deaths), with the respective \( P \) value reported as not significant.32 Therefore, from a “purist” perspective, based on failure to achieve statistical significance in the primary end point, DIGAMI was a negative trial. However, subsequent analyses of mortality at both 1 year and 3.5 years of follow-up showed statistically significant reductions in all-cause mortality in the insulin-treated group.32,33 If one accepts the validity of the mortality reduction observed in the longer-term analyses, the relative contributions of the various aspects of the trial remain uncertain, including (1) the effects of the short-term dextrose-insulin infusion and (2) the effects of multidose insulin injection in the outpatient setting. Therefore, although the DIGAMI data are the most compelling in the field of targeted glucose control for the treatment of ACS, the validity of the observations and the relative attribution of improved survival to short-term, in-hospital glucose lowering remain uncertain.

Beyond DIGAMI, a few other studies satisfy some (but not all) of the proposed parameters of validity and generalizability with regard to targeted glycemic control in the ACS setting. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) trial was designed to assess the effect of dextrose-insulin infusion versus usual care in patients with MI and hyperglycemia on arrival. Similar to DIGAMI, the therapeutic target for the insulin arm was 72 to 180 mg/dL, and intravenous dextrose (either D5W or D10W) was infused with the insulin; however, the insulin dose was much lower in HI-5 at 2 U/h (contrasted with 5 U/h used both in DIGAMI and in most trials of GIK therapy).34 The HI-5 trial was terminated early because of slow enrollment and failed to achieve a statistically significant difference in glucose values between the intensive and conventional glucose groups (149 versus 162 mg/dL 24 hours after randomization; \( P=NS \)).18 Mortality assessments at hospital discharge, 30 days, and 6 months all numerically favored usual care over targeted glucose control with insulin treatment, although none of these comparisons were statistically significant because of very low numbers of evaluable events (6 months, 10 versus 7 deaths; \( P=0.62 \)).

The DIGAMI-2 multicenter study attempted to determine whether potential survival benefit seen with targeted glucose control in the original DIGAMI study was primarily attributable to short-term or long-term glucose lowering with insulin.35 In DIGAMI-2, 1253 patients with AMI and diabetes mellitus or admission glucose \( >198 \) mg/dL were randomized to 1 of the 3 subgroups, as follows: (1) 24-hour insulin-glucose infusion targeting glucose of 126 to 180 mg/dL, followed by a subcutaneous insulin-based long-term glucose control (group 1, identical to the original DIGAMI intervention group); (2) same 24-hour insulin-glucose infusion but followed by standard glucose control (group 2); and (3) routine glucose management (group 3). Of note, the trial planned to recruit 3000 patients and was stopped prematurely because of slow recruitment. Glucose levels on arrival were similar between the 3 arms (\( \approx229 \) mg/dL). At 24 hours after randomization, glucose levels were modestly lower in the 2

### Table. Clinical Trials of Glucose Control in ACS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Targeted Glucose Control</th>
<th>Elevated Blood Glucose on Entry</th>
<th>Glucose Targets Specified</th>
<th>Blood Glucose Contrast Achieved</th>
<th>Clinical End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI (1995)</td>
<td>+/-</td>
<td>+; ( \approx280 ) mg/dL</td>
<td>+; 126–180 mg/dL vs usual</td>
<td>(+/-; 173 vs 211 mg/dL during first 24 h, difference in A1C but not fasting blood glucose afterward)</td>
<td>+</td>
<td>+/-; mortality neutral at 3 mo (primary end point), improved survival in glucose control arm by 1 y</td>
</tr>
<tr>
<td>Pol-GIK (1999)</td>
<td>-</td>
<td>-; 124 mg/dL</td>
<td></td>
<td>N/A; 106 vs 112 mg/dL in intervention vs control arms</td>
<td>+</td>
<td>Significantly higher mortality in intervention vs control arm at 35 d</td>
</tr>
<tr>
<td>DIGAMI2 (2005)</td>
<td>+/-</td>
<td>+; 229 mg/dL</td>
<td>+; 126–180 mg/dL in-hospital vs usual care acutely, 90–126 mg/dL fasting blood glucose vs usual care afterward</td>
<td>(+/-; 164 vs 180 mg/dL at 24 h, no difference afterward)</td>
<td>+</td>
<td>-; mortality neutral between 3 groups</td>
</tr>
<tr>
<td>CREATE-ECLA (2005)</td>
<td>-</td>
<td>+; 162 mg/dL</td>
<td></td>
<td>N/A; glucose higher in intervention arm vs control (187 vs 148 mg/dL)</td>
<td>+</td>
<td>Mortality neutral</td>
</tr>
<tr>
<td>HI-5 (2006)</td>
<td>+/-</td>
<td>+; ( \approx198 ) mg/dL</td>
<td>+; 72–180 mg/dL vs usual care</td>
<td>-</td>
<td>+</td>
<td>-; mortality neutral in-hospital, at 3 and 6 mo</td>
</tr>
</tbody>
</table>

N/A indicates not applicable.
groups assigned to short-term glucose lowering versus control (164 versus 180 mg/dL; \( P < 0.01 \)). This difference, although statistically significant, was clinically small and considerably less than expected; it was also much smaller than that observed in the original DIGAMI study. There was no difference in either glucose or HbA1C levels between the 3 groups at any other time point, with up to 3 years of follow-up. Importantly, on average, patients in group 1 failed to achieve the targeted fasting glucose range of 90 to 126 mg/dL during the outpatient management phase. Mortality over 2 years was not statistically different between the 3 groups (23.4% versus 21.2% and 17.9% in groups 1, 2, and 3, respectively; \( P = 0.83 \) for group 1 versus group 2; \( P = 0.16 \) for group 1 versus group 3). Because of its limitations (primarily lack of substantial contrast in glucose levels between the 3 groups), the DIGAMI-2 study did not provide a definitive answer in regard to whether targeted glucose lowering (whether short term or long term) has any clinical value in patients with AMI.

The remaining trials evaluating the effects of insulin infusion on clinical outcomes in the ACS setting have predominantly tested the GIK hypothesis (ie, hyperinsulinemic, hyperglycemic therapy), as summarized in published quantitative analyses, and have little to do with target-driven glucose control. Studies like the Glucose-Insulin-Potassium (GIPS) trial or the much larger Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) and the Organization for Revascularization and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation—Estudios Cardiologicos Latinoamerica (CREATE-ECLA) and the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)-6 trials (which in total randomized nearly 23,000 participants) assigned patients to fixed-dose GIK infusion regardless of their initial glucose values or diabetes mellitus status and did not prespecify targets for glucose control. In these studies, as dictated by the infusion protocols, high-dose delivery of insulin was supported by intravenous glucose administration to affect modest hyperglycemia, defined by protocol as a range of 126 to 198 mg/dL. For example, in the CREATE-ECLA trial, which enrolled >20,000 patients with AMI and demonstrated no discernible benefit with GIK therapy, 6-hour postrandomization glucose values were significantly higher in the GIK group than in the control group (187 versus 148 mg/dL). Thus, the GIK studies were not designed to evaluate targeted glucose control with insulin, and their findings should not be used in guiding decisions about glucose management in ACS.

The Poland Glucose-Insulin-Potassium (Pol-GIK) trial randomized 954 patients with AMI either to fixed “low-dose GIK,” which included a much lower rate of insulin infusion (0.8 to 1.3 U/h) than typical GIK regimens, or to normal saline infusion. Although it was not a typical GIK trial in that it used a much lower insulin dose, Pol-GIK cannot be considered a study of targeted glucose control either. First, it randomized patients who were on average normoglycemic at study entry (initial glucose \( \approx 124 \) mg/dL in both groups). It is therefore not entirely surprising that excess hypoglycemia was observed in the intervention arm, which required lowering of the fixed insulin dose during the conduct of the trial from 1.3 to 0.8 U/h. Second, and similar to other GIK studies, no glucose goals were prespecified or aimed for in this study, and the dose of GIK infusion was fixed and not adjusted to maintain a certain range of glucose values. As a result, there was no significant difference in glucose levels 24 hours after randomization (106 mg/dL in GIK versus 112 mg/dL in the control arm). The study was stopped prematurely because of excess mortality in the GIK arm at 35 days (8.9% versus 4.8% in the control arm; \( P = 0.01 \)). However, because of the serious limitations of interpretation stemming from the intent of the trial to evaluate the effect of fixed-dose administration of insulin rather than a targeted glucose control hypothesis, no valuable lessons can be learned about glucose lowering and patient outcomes in AMI on the basis of its results.

In summary, the clinical trial data for glucose control in ACS are scarce and inconclusive. In this context, one might be tempted to look for more definitive answers in the broader critical care field of patients in other clinical settings. In 2001, van den Bergh et al reported notable beneficial effects associated with normalization of blood glucose using insulin infusion compared with usual care among patients hospitalized in a surgical intensive care unit (ICU). These observations fueled enthusiasm among clinicians and professional societies to endorse a strategy of targeted glucose control across critically ill hospitalized populations. However, in the 8 years that followed, several additional randomized trials in various ICU patient populations have failed to reproduce these beneficial results.

Key among these more recent trials include the same investigators at the same institution using the same protocol as the surgical ICU trial, testing intensive glucose lowering in the medical ICU patients and showing lower morbidity but no difference in the trial primary end point of mortality with intensive glucose lowering versus usual care. In addition, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which was the largest trial of targeted glucose control in critically ill patients across ICU settings, demonstrated significantly higher mortality with intensive versus more conservative glucose control. These results have substantially tempered enthusiasm for aggressive glucose lowering in the ICU setting. However, the results of the NICE-SUGAR trial need to be interpreted in the context of the study design; the NICE-SUGAR trial compared “very intensive” glucose control with “good” glucose control and not “usual care.” Specifically, an intravenous insulin protocol was used in more than two thirds of patients in the control arm, producing an average glucose level of \( \approx 142 \) mg/dL. This degree of glucose control is more intensive than that achieved in control groups of other critical care studies, is lower than that achieved in the intensive arm of most ACS studies, and is much lower than that typically seen in routine clinical care. Thus, the most appropriate conclusion from the NICE-SUGAR study is that “good” glucose control (with values somewhere between 140 and 180 mg/dL) is sufficient, and more aggressive glucose lowering provides no additive benefit and may even be harmful.

Extrapolation of observations from trials outside of the ACS setting can also be problematic. Specifically, the findings from patients hospitalized with surgical illness, trauma, and sepsis cannot be simply extended to those with ACS. The
pathophysiology of these conditions is different, and the treatment thresholds and targets may be distinct as well. Prior studies have shown that the relationship between glucose values and mortality may vary significantly across various cardiovascular conditions\(^7\)\(^{-46}\); thus, it can also vary substantially between cardiac and noncardiac disease states.

### Ongoing Studies of Glucose Management in ACS

Several clinical trials of glucose management in ACS are currently ongoing. Although these studies may offer additional insights, they will not provide definitive answers in regard to clinical effectiveness and safety of target-driven glucose control in patients hospitalized with ACS.

The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care Trial (IMMEDIATE) is a National Institutes of Health—sponsored, randomized, placebo-controlled, double-blind, multicenter clinical trial of GIK infusion (1.5 mL/kg per hour, continuous infusion for total of 12 hours) administered as early as possible in the setting of suspected ACS in the prehospital emergency medical service setting.\(^47\) The primary hypothesis is that early GIK administration will prevent or reduce the size of AMI. Major secondary hypotheses are that GIK infusion will reduce mortality (at 30 days and 1 year) and reduce prehospital or in-hospital cardiac arrest and the propensity for heart failure. The trial plans to enroll 880 patients by April 2011. IMMEDIATE is specifically designed to test the GIK hypothesis and is not a study of targeted glucose control in ACS. Similar to previous GIK trials, the presence of hyperglycemia is not required as an inclusion criterion, and there are no prespecified goals for glucose control.

The International Multicenter Randomized Controlled Trial of Intensive Insulin Therapy Targeting Normoglycemia In Acute Myocardial Infarction: RESearching Coronary REDuction by Appropriately Targeting Euglycemia (RECREATE) is an ongoing randomized, open-label pilot study of targeted glucose control in patients with ST-segment elevation MI.\(^48\) Patients presenting with an initial glucose value \(\geq 144\) mg/dL are randomly assigned to either intensive glucose control or usual care. Patients in the intensive arm are treated with intravenous infusion of insulin glulisine for at least 24 hours and for as long as coronary care unit–level care is required, with a target glucose range of 90 to 118 mg/dL. Once transferred to the ward, patients in the intensive arm are switched to insulin glargine and continue this treatment for a total duration of 30 days after randomization. Patients in the control arm receive usual care for AMI, according to the local practice of each participating center. Because RECREATE is a pilot study designed to demonstrate the feasibility of targeted glucose control in ST-segment elevation MI, the primary end point is 24-hour difference in mean glucose between the 2 study groups. Although a number of secondary efficacy and safety end points will be explored (including all-cause and cardiovascular mortality, nonfatal recurrent MI, nonfatal stroke, rehospitalization for heart failure, and hypoglycemia), the study will likely lack statistical power to provide definitive answers in regard to clinical outcomes. The RECREATE study is expected to recruit 500 patients and is planned to finish enrollment in 2010.

### Prognostic Importance of Hypoglycemia in Patients With ACS

Because therapy of hyperglycemia in the hospital necessitates the use of insulin, it is inevitable that glucose lowering in the inpatient setting will produce excess hypoglycemia. Several studies suggested that glucose values in the hypoglycemic range may adversely affect mortality in ACS (93% increase in the adjusted odds of 2-year mortality in 1 study)\(^25\)\(^,\)\(^45\) and demonstrated a J-shaped relationship between average glucose values during hospitalization and in-hospital mortality (Figure 1).\(^21\) Whether hypoglycemia is directly harmful in patients with ACS or whether it is simply a marker for the most critically ill patients was recently evaluated in a large observational study.\(^50\) The authors showed that the risk associated with low blood glucose was confined to those who developed hypoglycemia spontaneously, most likely as the result of severe underlying illness. In contrast, hypoglycemia that occurred after insulin initiation was not associated with worse survival. Two subsequent analyses of data from the DIGAMI-2 and CREATE-ECLA trials also found no significant association between hypoglycemia and mortality, after adjustment for confounders.\(^51\)\(^,\)\(^52\) These findings suggest that hypoglycemia is a marker of severe illness rather than a direct cause of adverse outcomes. Although continuous efforts to avoid hypoglycemia are certainly warranted, these studies cast some doubt on the assumption that the lack of clinical benefit from intensive glycemic control in clinical trials is simply a consequence of excess hypoglycemia.

### Current Patterns of Glucose Control in ACS

The current practice of glucose management in the United States is highly variable.\(^31\) Large proportions of ACS patients with hyperglycemia do not receive glucose-lowering therapy, even in the setting of marked hyperglycemia (Figure 3); this is particularly evident among those without known diabetes mellitus.\(^7\)\(^,\)\(^26\) A recent study from the United Kingdom showed that 64% of patients without diabetes mellitus with admission glucose
≥11 mmol/L (≈200 mg/dL) received no glucose-lowering treatments during hospitalization. Many factors contribute to this inconsistency of clinical practice, such as the lack of convincing clinical outcomes data, concerns about hypoglycemia, institutional barriers, and clinical inertia, underscoring the importance of continued investigation with regard to the efficacy and safety of glucose management in the setting of ACS.

Summary and Recommendations
There is a clear and urgent need for well-designed, large-scale clinical outcome trials of target-driven glucose control in ACS with sufficient statistical power to detect a clinically important difference in mortality and other adverse clinical outcomes. Until such trials are completed, any specific recommendations in regard to glucose management in ACS are based on epidemiological observations, mechanistic hypotheses, and expert consensus and are not grounded in solid clinical evidence.

Reflecting this uncertainty, in 2008 the American Heart Association published an update on its position relative to glucose targets for ACS/MI patients, which substantially liberalized previous recommendations. This American Heart Association position advocates for a glucose treatment threshold of >180 mg/dL. A similar position was adopted by the 2009 focused update of ST-segment elevation MI guidelines and was also endorsed by the revised American Association of Clinical Endocrinologists/American Diabetes Association guidelines. These guidelines now recommend the same glucose threshold for therapeutic intervention in critically ill patients of >180 mg/dL, with the suggested therapeutic target of glucose control specified at 140 to 180 mg/dL, a substantially more liberal approach than prior documents. Although even these targets represent an expert consensus, it is likely the most prudent approach in the presence of the accumulated data.

Until more information becomes available, several practical suggestions are reasonable in regard to glucose management during ACS hospitalization, as follows:

1. Assessment of glucose values at the time of admission and glucose monitoring during hospitalization will provide useful information in regard to risk stratification and prognosis. Thus, it should be pursued regardless of whether treatment is being considered.

2. If targeted glucose control is being considered, several precautions should be observed:
   a. Conservative treatment initiation thresholds and glucose targets (as outlined above) should be used, in agreement with the recommendations of professional societies. Very aggressive glucose lowering, including “normalization of blood glucose” as previously recommended, does not clearly offer additional benefit and may be harmful on the basis of existing data.
   b. Evidence-based protocols should be used when and if glucose control strategies are implemented. Such protocols should:
      i. incorporate the rate of change in glucose values as well as insulin sensitivity in determination of insulin infusion rates and adjustments;
      ii. provide specific directions on the frequency of glucose testing and hypoglycemia management.

3. Finally, and most importantly, continued efforts are necessary for the design and execution of definitive clinical trials assessing glucose control targets, therapies, and timing so that more evidence-based recommendations may be provided to clinicians in regard to glucose management during ACS.

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References
glycemic control reduces heart inflammation and remodeling during acute myocardial infarction.


Key Words: diabetes mellitus ■ epidemiology ■ glucose ■ insulin ■ myocardial infarction
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