# Management of Blood Glucose in Patients With Acute Coronary Syndromes

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Hyperglycemia during admission for acute myocardial infarction (MI) is common and associated with poor outcomes. Prior studies employed two distinct approaches to improve outcomes in patients with acute MI—one focused on glucose control, and the other on provision of glucose, insulin, and potassium. However, despite multiple large-scale studies, the benefits of glucose lowering in the setting of acute MI remain unclear. This article reviews data from observational studies and clinical trials and synthesizes this information into practical recommendations based on available evidence.

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**KEY WORDS**

Hyperglycemia • Acute myocardial infarction • Acute coronary syndromes • Diabetes mellitus • Glucose-insulin-potassium

Hyperglycemia during admission for acute myocardial infarction (MI) is common and associated with poor outcomes. However, data with regard to the benefits of glucose lowering in this setting are inconclusive. It is therefore not surprising that the management of glucose control during hospitalization for acute MI remains highly variable in the United States, with more than one-third of patients with sustained severe hyperglycemia (mean glucose ≥ 200 mg/dL) receiving no insulin therapy.[1]

## Observational Studies

Patients with diabetes mellitus are at increased risk for coronary artery disease and have worse in-hospital outcomes following an acute coronary event when compared with nondiabetic patients.

Several studies have now shown that patients with diabetes have higher rates of heart and renal failure, cardiogenic shock, arrhythmia, reinfarction, and in-hospital mortality when admitted with an acute MI.[2-4] These differences may reflect a greater extent of coronary heart disease and ventricular dysfunction in patients with diabetes, but may additionally result from decreased utilization of evidence-based therapies, such as thrombolysis and percutaneous coronary intervention in this subgroup of patients. The disparity in outcomes following acute MI between patients with and without diabetes has subsequently led to greater interest in the effects of hyperglycemia on the heart during acute coronary syndromes (ACS).

Extensive literature now documents that hyperglycemia at the time of admission for acute MI is associated with higher in-hospital mortality.[5-7] More recently, persistent hyperglycemia, as denoted by mean blood glucose during hospitalization, has been found to be more strongly associated with mortality than a single admission blood glucose measurement.[8] Additionally, the relationship between mean blood glucose and mortality is J-shaped, with increased risk for in-hospital death among patients with persistent hypoglycemia and hyperglycemia. Patients with mean blood glucose values between 70 and 120 mg/dL are at lowest risk for mortality.

The association between hyperglycemia and adverse outcomes appears similar in patients with ST-elevation MI (STEMI) and non–STEMI (NSTEMI). Among patients with STEMI, hyperglycemia correlates with infarct size[9] and is associated with increased short-term mortality.[10,11] Among patients with NSTEMI, admission hyperglycemia is also associated with adverse clinical outcomes, including mortality.[6,8,12]

Importantly, the relationship between mean and admission blood glucose and mortality is stronger in patients without recognized diabetes.[8] Mortality risk for patients with diabetes appears to rise only when glucose values well exceed 200 mg/dL. The reasons for these differences are unclear. Patients with diabetes may be less vulnerable to acute hyperglycemia during MI as a result of long-standing preexisting hyperglycemia through as yet-unidentified mechanisms. On the other hand, acute hyperglycemia during MI frequently denotes previously unrecognized diabetes.[13-15] Hyperglycemic patients without recognized diabetes at the time of admission may have received less or suboptimal medical care prior to their event, which may result in subsequent poor outcomes.

***Mortality risk for patients with diabetes appears to rise only when glucose values well exceed 200 mg/dL.***

Is there a pathophysiologic basis for the relationship between hyperglycemia and mortality at the time of ACS? ACS is associated with high levels of serum catecholamine, glucagon, and cortisol.[16,17] These counter-regulatory hormones result in insulin resistance, lower utilization of glucose for metabolism, and a shift toward oxidation of fatty acids instead of anaerobic glucose metabolism.[18] The shift to fatty acid metabolism, which requires oxygen, increases oxygen demand and may exacerbate myocardial ischemia.[19] In addition, high levels of free fatty acids and their intermediates may be directly toxic to the myocardium.[19] Therefore, the acute phase response during an MI contributes to disorders of glucose metabolism.

In turn, hyperglycemia during an acute coronary event, whether resulting from the stress response, preexisting or new disorders of glucose metabolism, appears to be harmful to the myocardium. Acute hyperglycemia results in increased levels of free radicals, suppression of endothelium-dependent vasodilation, and reduced left ventricular function.[20,21] It is also associated with the induction of various inflammatory mediators that are toxic to the myocardium,[22,23] and with the development of a prothrombotic state with increased platelet aggregation.[24] Interestingly, a recent study suggests that low high-density lipoprotein (HDL) cholesterol is associated with a delayed recovery of stress hyperglycemia, and reduced insulin secretion and sensitivity induced during acute phase of MI.[25] The exact interaction between HDL and hyperglycemia will need to be further explored. The effects of hyperglycemia on the myocardium are depicted in Figure 1.

Given that glucose disorders both arise from and contribute to myocardial damage, the exact effects of glucose lowering on outcomes following MI are difficult to predict. One large observational study suggests that normalization of glucose values in patients with acute MI after admission is associated with better survival.[26] Patients with higher mean postadmission values are at progressively increased risk for in-hospital death compared with patients with postadmission values $< 110$ mg/dL. This relationship is similar in patients treated with insulin therapy (subcutaneous or intravenous) and in patients whose glucose levels return to normal spontaneously. This observation suggests that the effects of blood glucose lowering during acute MI should be evaluated in clinical trials.

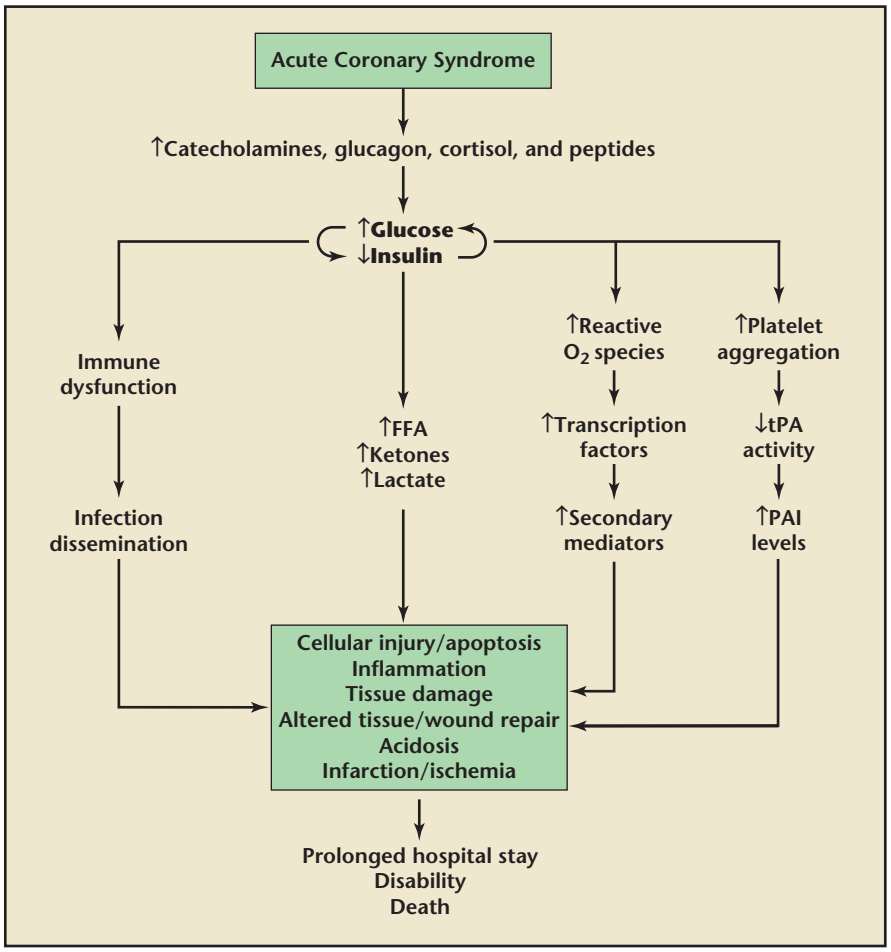


**Figure 1.** Pathophysiology of hyperglycemia during acute myocardial infarction. FFA, free fatty acids; PAI, plasminogen activator inhibitor; tPA, tissue type. Adapted with permission from Deedwania P et al.[37]

So far, we have delineated an epidemiologic relationship between hyperglycemia and adverse outcomes and described plausible mechanisms that may explain the association. However, it remains unclear whether hyperglycemia is a marker or mediator of adverse outcomes and whether pharmacologic treatment to lower blood glucose levels translates into improved outcomes. Only rigorously conducted randomized controlled trials can potentially answer this question.

## Randomized Clinical Trials: Two Distinct Approaches

Several randomized clinical trials have investigated the role of management of glucose disorders during an ACS. Two separate approaches have been tried. One strategy focuses on targeted glucose control with insulin during acute MI. This approach may be limited by the risk of hypoglycemia, but has the potential benefit of mitigating negative effects of hyperglycemia on the myocardium. In addition, provision of insulin may decrease free fatty oxidation and minimize their toxic effects on the heart. Another approach is to treat patients with the provision of glucose, insulin, and potassium (GIK) at a fixed dose. The primary goal is to shift metabolism toward glucose utilization and away from fatty acid oxidation, rather than to control glucose. This approach is thought to have several potential benefits, including lowering of myocardial oxygen demand, increase in myocardial glycogen stores, supression of free fatty acid levels and blunting their toxic effects on the myocardium, and improved calcium and sodium homeostasis. However, it may be associated with increased fluid gain and rapid electrolyte shifts, as well as exacerbation of hyperglycemia if glucose levels are allowed to rise.

## Approach 1: Control of Hyperglycemia

### *Acute MI Trials*

**DIGAMI.** The largest randomized controlled trial to test the glucose control hypothesis was the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. The trial enrolled 620 patients at 19 Swedish coronary care units between 1990 and 1993.[27] All patients had a suspected acute MI within the preceding 24 hours and known diabetes or blood glucose levels $>200$ mg/dL.[27] Patients were randomized to insulin-glucose infusion for at least 24 hours followed by subcutaneous insulin four times daily for at least 3 months, with the target blood glucose level between 126 and 196 mg/dL versus usual care. Blood glucose levels were significantly lower with insulin infusion at 24 hours (173 vs 211 mg/dL) and at hospital discharge (148 vs 162 mg/dL) with a lower hemoglobin $A_{1c}$ ($HbA_{1c}$) in the treated group at 3 months (7.0% vs 7.5%; $P < .01$). The primary outcome of the study was all-cause mortality at 3 months, which was 12.4% in the infusion group and 15.6% in the control group ($P$ = NS). However, the difference in mortality was significant at 1 year (18.6% vs 26.1% for infusion and control groups, respectively; $P = .027$) and persisted at 3.4-year follow-up (33% vs 44%; $P = .011$) (Table 1).[28]

Although the study showed improvements in mortality at 1- and 3.4-year follow-up in the glucose infusion group, it is difficult

**TABLE 1**

**Results of Randomized Controlled Trials Using Approach 1: Control of Hyperglycemia**

| Trial Name | Participants | Intervention | Primary Outcome | Comments |
|---|---|---|---|---|
| Acute MI Trials | | | | |
| DIGAMI[27] 1990-1993 | Suspected acute MI within 24 h, known DM, and glucose $\geq$ 198 mg/dL or glucose $\geq$ 198 mg/dL without known DM (n = 620) | Insulin-glucose infusion (80 U insulin, 5% glucose), target 126-196 mg/dL, followed by subcutaneous insulin 4 $\times$ daily $\times \geq$ 3 mo; control: insulin if deemed clinically indicated | 3-mo mortality: 12.4% infusion group vs 15.6% control ($P$ = NS); 1-y mortality: 18.6% vs 26.1% ($P$ = .027); 3.4-y mortality: 33% vs 44% ($P$ = .011) | Small sample size (lower than expected mortality); inability to distinguish the effect of insulin infusion vs subcutaneous insulin administered thereafter |
| DIGAMI-2[29] 1998-2003 | Suspected acute MI, admitted to participating coronary care units, established DM or admission glucose > 198 mg/dL (n = 1253) | Group 1: 24-h insulin-glucose infusion (target 126-180 mg/dL) followed by subcutaneous insulin based therapy (target fasting glucose 90-126 mg/dL, nonfasting < 180 mg/dL); Group 2: 24-h insulin-glucose infusion (target 126-180 mg/dL) followed by standard control; Group 3: routine management according to local practice | 2-y mortality: 23.4% group 1 vs 21.2% group 2 ($P$ = .83) vs 17.9% group 3 ($P$ = .16 compared with group 1) | Did not achieve target blood glucose levels; no statistical difference between blood glucose levels achieved in the 3 groups |
| HI-5[30] 2001-2004 | Acute MI within 24 h, known DM or admission blood glucose $\geq$ 140 mg/dL (n = 240) | Insulin at 2 U/h and 5% dextrose at 80 ml/h (titrate to 72-180 mg/dL) $\times$ 24 h; control: usual DM therapy | Inpatient mortality: 4.8% insulin vs 3.5% control ($P$ = .75); 3-mo mortality: 7.1% vs 4.4% ($P$ = .42); 6-mo mortality: 7.9 vs 6.1% ($P$ = .62) | Significant difference in blood glucose between groups was not achieved; small study sample |
| Non–Acute MI Trials | | | | |
| NICE-SUGAR[31] | Critically ill patients, expected to require ICU for $\geq$ 3 d (n = 6104) | Insulin infusion to target glucose 81-108 mg/dL; control: insulin infusion to target glucose $\leq$ 180 mg/dL | 90-d all-cause mortality: 27.5% intensive vs 24.9% control ($P$ = .02) | Increased 90-d mortality in the intensively treated patients; very few patients admitted to ICU with diagnosis of acute MI (n = 43) |
| Leuven SICU study[24] | Patients admitted to ICU primarily for surgical reasons, receiving mechanical ventilation (n = 1548) | Insulin infusion to target glucose 80 to 110 mg/dL; conventional: insulin for glucose > 215 mg/dL with target 180 to 200 mg/dL | All-cause mortality during intensive care: 4.6% intensive vs 8.0% conventional ($P$ < .04) | Surgical ICU patients |
| Leuven MICU study[25] | Medical ICU patients expected to require ICU care for $\geq$ 3 d (n = 1200) | Intensive: insulin infusion to target glucose 80-110 mg/dL; conventional: insulin for glucose > 215 mg/dL with target $\leq$ 180 mg/dL | In-hospital all-cause mortality: 37.3% intensive vs 40% conventional ($P$ = .33) | Intensive treatment associated with reduced morbidity; only 4% of patients admitted for cardiac causes |

DIGAMI, Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction; DM, diabetes mellitus; HI-5, Hyperglycemia: Intensive Insulin Infusion in Infarction; ICU, intensive care unit; MI, myocardial infarction; MICU, medical intensive care unit; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation; NS, not significant; SICU, surgical intensive care unit; U, units.

to know whether the difference is attributable to the insulin infusion during acute phase versus the subsequent treatment of hyperglycemia with subcutaneous injections. In addition, the trial was relatively small and was conducted at a time when modern evidence-based interventions in acute MI were just beginning to emerge, limiting our ability to generalize these conclusions to the era of current acute MI strategies.

**DIGAMI-2.** In order to clarify whether mortality benefit seen in DIGAMI was due to glucose-insulin infusion during acute MI versus glucose control thereafter, the DIGAMI-2 trial randomized 1253 patients with established diabetes or admission blood glucose $>$ 200 mg/dL to three groups: (1) glucose-insulin infusion with a target glucose between 126 and 180 mg/dL for at least 24 hours followed by long-term treatment with subcutaneous insulin (short-acting prior to meals and intermediate-acting in the evening) with a target fasting glucose between 90 and 126 mg/dL and nonfasting glucose $<$180 mg/dL; (2) glucose-insulin infusion as described above with glucose-lowering thereafter left at the discretion of the physician; and (3) control group with no established glucose targets.[29] Blood glucose was slightly lower in group 1 and 2 compared with group 3 at 24 hours, but differences in blood glucose and $HbA_{1c}$ levels were not significantly different between the three groups thereafter and did not reach prespecified targets. The primary endpoint of all-cause mortality did not differ between the three groups at median follow-up of 2.1 years (23.4% in group 1, 22.6% in group 2, and 19.3% in group 3; $P$ = NS). There were also no differences in rates of reinfarction and stroke among the groups.

The DIGAMI-2 trial found no differences associated with glucose infusion or subsequent insulin administration in a population of patients similar to those recruited in the DIGAMI trial. However, there were no differences in glucose control between the three groups and prespecified targets for glucose levels were not attained. In addition, the event rate was lower than expected and the trial was stopped earlier than planned due to difficulty with recruitment; therefore, it was underpowered to establish significant differences in mortality.

**HI-5.** The goal of the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study was to determine whether control of hyperglycemia during acute MI will improve mortality among patients with diabetes or those presenting with elevated blood glucose levels ($\geq$ 140 mg/dL).[30] Eligible subjects had to have a positive troponin-T within the last 24 hours or ST-segment elevation on electrocardiography. Of 240 participants, 126 subjects were randomized to the insulin infusion with a goal to maintain blood glucose in the 72 to 180 mg/dL range for at least 24 hours. Conventionally treated control patients received usual therapy and short-acting insulin was permitted if severe hyperglycemia ($>$ 288 mg/dL) ensued. There were no differences in blood glucose levels at 24 hours and no differences in $HbA_{1c}$ levels among patients with diabetes at 3 and 6 months among the groups. The primary outcome of all-cause mortality did not differ between the groups during hospitalization or at 3 and 6 months. The secondary endpoints of cardiac failure and reinfarction were lower in the infusion group.

The HI-5 study showed no benefit to the variable dose insulin infusion strategy on short-term mortality. However, similar to the DIGAMI-2, this study's glucose targets were not achieved. Therefore, the question of whether strict glycemic control in the peri-infarct period can result in improved outcomes after acute MI remains unanswered.

### *Nonacute MI Trials*

Several studies have also investigated tight glycemic control in the intensive care unit setting. Although these studies were not designed to specifically address glucose control in acute MI, they provide important insights among critically ill patients.

**NICE-SUGAR.** In the largest study to date, Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, over 6000 critically ill patients were randomized to intensive glucose control (target, 81-108 mg/dL) or conventional glucose control (target, $\leq$180 mg/dL) in a multicenter, multinational trial.[31] Control of blood glucose was achieved with an insulin infusion, with the mean blood glucose of 115 and 144 mg/dL attained in the intensively and conventionally treated arms, respectively. Intensive glucose control was actually associated with a higher risk for the primary endpoint, death from any cause within 90 days (odds ratio 1.14; 95% confidence interval [CI], 1.02-1.28); this effect was similar for medical and surgical patients. Deaths from cardiovascular causes were more common in the intensive control group (41.6%) than in the conventional control group (35.8%; $P$ = .02), as was severe hypoglycemia (6.8% vs 0.5%; $P <$ .001). The precise reason for the increased mortality in the intensively treated group is unknown. Although the study provides important evidence for treatment of hyperglycemia in critically ill

patients, it is problematic to apply the findings to patients with acute MI as the number of patients with this diagnosis on admission was very small (n = 43).

**The Leuven Surgical ICU Study.** The findings from NICE-SUGAR contrast with an earlier study published in 2001 by Van den Berghe and colleagues,[32] which showed that intensive glucose control in the surgical intensive care unit (ICU) was associated with reduced mortality and morbidity. In this single-center study, 1548 patients were randomized to insulin infusion with a glucose target of 80 to 110 mg/dL or insulin infusion only when blood glucose exceeded 215 mg/dL, with a target of 180 to 200 mg/dL. In this study, intensive insulin therapy was associated with a 42% relative reduction in ICU mortality. Tight glucose control was also associated with reductions in bloodstream infections, acute renal failure requiring dialysis or hemofiltration, median number of erythrocyte transfusions, critical illness polyneuropathy, and prolonged mechanical ventilation and intensive care. However, all participants in this study were surgical patients.

**The Leuven Medical ICU Study.** Another study by Van den Berghe and colleagues,[33] of 1200 patients similarly randomized to intensive glucose control (target 80-110 mg/dL) versus conventional control (insulin for glucose $>215$ mg/dL with goal $<180$ mg/dL) in a single-center medical ICU trial, showed no difference with respect to in-hospital mortality (37.3% vs 40% in the intensive and conventional groups, respectively; $P = .33$). However, intensive glucose control was associated with reduced risk for some of the secondary outcomes of morbidity (days in the ICU, days in the hospital, newly acquired kidney injury, and days to weaning from mechanical ventilation). Only approximately 4% of these patients were admitted to the ICU for cardiovascular diagnoses.

### *Meta-Analysis*

A recent meta-analysis of 26 trials in the ICU setting (including the NICE-SUGAR trial) showed a pooled relative risk of death at 0.93 (95% CI, 0.83-1.04) for intensive versus conventional glucose control.[34] The specific ICU setting appeared to influence the findings, with data from surgical ICUs showing benefit with intensive insulin therapy (relative risk, 0.63; 95% CI, 0.44-0.91), whereas data from medical and mixed critical care settings showed no such benefit. Overall, the conclusions from the meta-analysis were that intensive insulin therapy increased the risk of hypoglycemia but provided no overall benefit on mortality in the critically ill, although a possible mortality benefit to patients admitted to the surgical ICU was suggested.

Taken together, these data suggest that critically ill medical patients may benefit from glucose control but the optimal targets are likely to lie in the 140 to 180 mg/dL range, with potential harm in the $<110$ mg/dL range.[35-37] However, it is problematic to extrapolate these findings to critically ill patients with acute MI because few patients in the ICU studies had this diagnosis.

## Approach 2: Delivery of Glucose, Insulin, and Potassium

### *ECLA*

The pilot trial Estudios Cardiologicos Latinoamerica (ECLA) recruited 407 patients regardless of blood glucose or diabetes status with suspected acute MI within 24 hours of symptom onset.[38] Patients were randomized to high- or low-dose GIK infusion at fixed doses for 24 hours, or to standard management. There were no significant differences in glucose levels at 6, 24, and 48 hours after randomization between the groups. Although the primary endpoint of the study was not stated, in-hospital mortality did not differ between the GIK infusion groups and control subjects (6.7% vs 11.5%; $P$ = NS). In a nonprespecified subgroup of patients receiving reperfusion therapy, GIK infusion was associated with decreased in-hospital death (Table 2).

The pilot trial showed no differences in short-term mortality associated with the fixed-dose glucose-insulin infusion and generated a hypothesis that the infusion may benefit patients specifically undergoing reperfusion for acute MI. However, the high in-hospital mortality rate among patients receiving reperfusion therapy compared with those patients who were not reperfused suggests nonrandomized allocation to reperfusion. These mortality rates and the differences across reperfusion status are not consistent with prior literature, thus raising some questions about the trial's findings.

### *Pol-GIK*

The Polish-Glucose-Insulin-Potassium (Pol-GIK) trial similarly evaluated low-dose GIK infusion for 24 hours versus normal saline infusion in patients with suspected acute MI within 24 hours of symptoms.[39] Patients with diabetes requiring insulin, those with renal insufficiency, and those with severe pulmonary congestion were excluded. During prespecified interim analysis of 954 patients, cardiac mortality at 35 days did not differ between the groups

**TABLE 2**

**Results of Randomized Controlled Trials Using Approach 2: Provision of Glucose-Insulin-Potassium**

| Trial Name | Participants | Intervention | Primary Outcome | Comments/Limitations |
|---|---|---|---|---|
| ECLA[38] 1998 | Suspected acute MI within 24 h (n = 407) | GIK: high dose: 25% glucose, 50 U insulin, 80 mmol KCl; low dose: 10% glucose, 20 U insulin, 80 mmol KCl × 24 h; control: usual care | In-hospital mortality: 6.7% GIK (high and low dose) vs 11.5% control (*P* = NS) | No significant differences observed in glucose levels between groups |
| Pol-GIK[39] 1994-1995 | Acute MI within 24 h, excluded DM requiring insulin treatment (n = 954) | GIK: 10% glucose, 32-20 U insulin, 80 mEq potassium × 24 h; control: normal saline | Cardiac death, cardiac events (cardiac arrest, congestive heart failure, reinfarction, arrhythmia and/or conduction disturbances, and angiography [PTCA, CABG]) at 35 d; cardiac deaths: 6.5% GIK vs 4.6% control (*P* = .20); cardiac events: GIK 43.3% vs control 41.7% (*P* = .62) | Relatively normal blood glucose at randomization, low-risk patients |
| GIPS[40] 1998-2001 | Acute MI within 24 h, STEMI (n = 940) | GIK: 20% glucose, 50 U insulin, 80 mmol KCl, target glucose 126-198 mg/dL; control: no infusion | 30-d mortality: 4.8% in GIK vs 5.8% control (*P* = NS) | Small sample size given low mortality |
| GIPS-2[41] | Acute MI within 24 h, STEMI, excluded heart failure patients (n = 889) | GIK: 20% glucose, 50 U insulin, 80 mmol KCl, target glucose 126-198 mg/dL; control: no infusion | 30-d mortality: 2.9% in GIK vs 1.8% control (*P* = NS) | |
| CREATE ECLA[42] 1998-2002 | Acute MI within 24 h, STEMI (n = 20,201) | GIK: high dose (25% glucose, 50 U insulin, 80 mEq KCl) × 24 h; control: no infusion | 30-d mortality: 10.0% GIK vs 9.7% control (*P* = .45) | Adequately powered to detect even small effect on mortality |
| OASIS-6/CREATE ECLA[43] 1998-2004 | Acute MI within 24 h, STEMI (n = 22,943) | GIK: high dose (25% glucose, 50 U insulin, 80 mEq KCl) × 24 h; control: no infusion | 30-d mortality: 9.7% GIK vs 9.3% control (*P* = .33) | 30-d mortality higher in the GIK group |

CABG, coronary artery bypass graft; CREATE, Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation; DM, diabetes mellitus; ECLA, Estudios Cardiologicos Latinoamerica; GIK, glucose-insulin-potassium; GIPS, Glucose-Insulin-Potassium Study; KCl, potassium chloride; MI, myocardial infarction; OASIS, Organization for the Assessment of Strategies for Ischemic Syndromes; Pol-GIK, Polish-Glucose-Insulin-Potassium; PTCA, percutaneous transluminal coronary angioplasty; STEMI, ST-elevation myocardial infarction; U, units.

(6.5% vs 4.6% for the infusion and control groups, respectively; $P$ = NS), but total mortality was significantly higher in the infusion group (8.9%) versus the control group (4.8%; $P$ = .01). The analysis of the interim data resulted in the decision to terminate the trial.

The Pol-GIK trial suggested no benefit and potential harm to glucose-insulin infusion therapy in patients with acute MI. Importantly, the average glucose at randomization was in the normal range (124 and 126 mg/dL in the GIK and control groups, respectively); therefore, it is not possible to extrapolate these findings to hyperglycemic patients. The mechanism for increased noncardiac mortality in the infusion group was unexplained and the authors postulated that it occurred by chance.

### *GIPS*

The Glucose-Insulin-Potassium Study (GIPS) randomized 940 patients irrespective of diabetes status or glucose levels who had an ST-elevation MI or new left bundle branch block (LBBB) to GIK infusion for 8 to 12 hours with a target glucose of 126 to 198 mg/dL or to no infusion.[40] Once the infusion was started, patients were sent to the catheterization laboratory for visualization of the coronary anatomy and reperfusion therapy. The primary endpoint of the study was 30-day mortality, which was not different between the groups (4.8% in the infusion group and 5.8% in the control group; $P$ = NS). Among six prespecified subgroups, only patients without heart failure appeared to have lower mortality in the infusion group (1.2% vs 4.2%; $P$ = .01), but neither adjustment for multiple comparisons nor interaction $P$ value were provided, making findings in the subgroups somewhat speculative. The subsequent GIPS-2 trial randomized 889 patients with acute STEMI and without heart failure to GIK infusion versus no infusion and found no difference in 30-day mortality between the groups (2.9% vs 1.8%).[41] Due to the small sample size of the two trials with events lower than expected, these studies did not answer the question of whether GIK management strategy reduces deaths following MI.

### *CREATE-ECLA*

Two large-scale clinical trials were merged together to settle the question of GIK infusion in acute MI definitively. The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) and the ECLA-2 GIK Full Scale Trial randomized 20,201 patients with acute STEMI or LBBB within 12 hours of symptoms onset to high-dose GIK infusion for 24 hours.[42] The infusion protocol did not target a particular glucose level and adjustments were made based on heart failure and potassium levels only. At 6 and 24 hours after randomization, blood glucose levels were higher in the infusion group (187 and 155 mg/dL) than in the control group (148 and 135 mg/dL); 83% of patients underwent reperfusion therapy. The primary endpoint of 30-day mortality was not different between the groups: 9.7% in control patients and 10.0% in infusion patients ($P$ = NS). The lack of benefit of the infusion was consistent across prespecified subgroups and also in secondary endpoints of cardiac arrest and cardiogenic shock.

This large multicenter trial evaluated the effects of high-dose glucose-insulin infusion on subsequent mortality and found no benefit associated with the infusion. The sample size of this trial is large enough to exclude a significant benefit of the infusion on mortality using this strategy.

### *OASIS-6 and Combined CREATE-ECLA/OASIS-6*

The Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) trial was terminated prematurely after the results of ECLA-CREATE showed neutral effects of GIK infusion on mortality. OASIS-6 planned to randomize 8000 patients with STEMI to the high-dose infusion in a similar manner to the CREATE-ECLA protocol. After 2748 patients were randomized, the study was terminated. When the data on these patients were added to the CREATE-ECLA trial, combined analysis revealed no difference in mortality at 30 days between groups (9.7% in the infusion group, 9.3% in the control group; $P$ = NS).[43] Higher levels of glucose, potassium, and net fluid gain were seen in the infusion group and may help explain the increased risk for death and heart failure observed in the infusion group at 3 days.

## Remaining Questions

Despite strong epidemiologic relationship between hyperglycemia and adverse outcomes, the trials aimed at targeted glucose control via insulin provision during acute MI are small, methodologically limited, and provide conflicting results. Due to the difficulty in achieving glucose targets in DIGAMI and HI-5 trials, their results leave open the question of whether tight peri-MI glucose control is beneficial. The GIK infusion approach, which is aimed at decreasing free fatty oxidation, showed early promise in smaller studies but no reduction in mortality in large-scale trials. Whether the hypothetical benefits of the insulin infusion are outweighed by deleterious effects of electrolyte shifts and fluid gain remains unclear, but GIK infusion during acute MI (as performed during the trials) does not appear warranted.

Additional concerns have recently been raised regarding hypoglycemia, which may occur in patients who pursue strict glycemic control. In randomized controlled trials, hypoglycemia occurs more frequently in patients treated intensively with insulin or insulin secretagogues, as compared with patients assigned to conventional glucose control strategies.[7,44-46] Observational studies suggest that hypoglycemia during acute MI hospitalization is associated with increased mortality.[10,47] However, this association may be confined to those individuals who develop hypoglycemia spontaneously. In a large prospective study of 7820 hyperglycemic patients with acute MI, hypoglycemia during hospitalization was associated with increased in-patient mortality only among those who did not receive any insulin during hospitalization (ie, spontaneous hypoglycemia).[48] In contrast, low blood glucose was not a significant predictor of death in individuals treated with insulin (iatrogenic hypoglycemia), suggesting that hypoglycemia may not lie in the causal pathway to the adverse outcome of death, but simply reflect underlying severity of illness. In the analysis of the DIGAMI-2 trial of 1253 acute MI patients with diabetes, hypoglycemia within the first 24 hours occurred more frequently in those treated with insulin (12%) than those assigned to routine management (1%), but mortality did not differ between those individuals with and without hypoglycemic episodes.[49] In a much larger post-hoc analysis of the combined CREATE-ECLA and OASIS-6 trial data, admission hypoglycemia was associated with increased 30-day mortality among 30,536 acute MI patients[50]; however, after 24 hours postadmission, hypoglycemia was no longer predictive of death. The findings from these analyses together suggest that hypoglycemia may not be mediating the adverse outcomes; rather, the occurrence of hypoglycemia may mark patients presenting with more severe degrees of illness. Nevertheless, continuing efforts to minimize in-patient hypoglycemia are obviously warranted and important.

*In a large prospective study of 7820 hyperglycemic patients with acute MI, hypoglycemia during hospitalization was associated with increased in-patient mortality only among those who did not receive any insulin during hospitalization.*

## Recommendations for Management

Given the lack of evidence for specific glucose targets during acute MI, existing recommendations rely on expert opinion and limited data. The 2008 American Heart Association (AHA) scientific statement outlined several recommendations, including obtaining admission glucose on patients with suspected acute MI, and treating severe hyperglycemia (> 180 mg/dL) as long as hypoglycemia can be avoided.[37] The 2009 American College of Cardiology/AHA guidelines for management of patients with STEMI similarly recommend avoidance of severe hyperglycemia (>180 mg/dL) as well as frank hypoglycemia with a weak recommendation to use insulin infusion.[51] The 2010 American Diabetes Association (ADA) guidelines and the 2009 ADA/American Association of Clinical Endocrinologists consensus statement recognize the epidemiological relationship between hyperglycemia and adverse outcomes in hospitalized patients but state that there is no clear evidence for specific blood glucose goals in noncritically ill patients.[35,36] Nevertheless, based on clinical experience and judgment, these guidelines suggest pre-meal blood glucose targets of < 140 mg/dL and random blood glucose < 180 mg/dL as long as such targets can be safely achieved (ie, without occurrence of hypoglycemia). The target for critically ill patients is consistent with the NICE-SUGAR study findings and lies between 140 to 180 mg/dL. Moreover, the ADA guidelines recommend insulin therapy as the preferred method of glucose control in the majority of hospitalized patients, with insulin infusion for patients in the ICU and subcutaneous insulin for all others. The most recent 2012 Endocrine Society clinical practice guidelines for hospitalized patients similarly recommend glucose monitoring with the following targets: pre-meal glucose < 140 mg/dL and a random blood glucose < 180 mg/dL (10.0 mmol/L) for the majority of hospitalized patients with noncritical illness.[52]

*… the ADA guidelines recommend insulin therapy as the preferred method of glucose control in the majority of hospitalized patients, with insulin infusion for patients in the ICU and subcutaneous insulin for all others.*

## Insulin Protocols

Various glucose control protocols have been developed in the critical care unit setting. Some of these have been tested and were found to be effective for lowering glucose levels and safe with regard to the risk of hypoglycemia.[53,54] Typically, protocols that take into account dynamic changes in glucose levels (ie, those that integrate the direction and magnitude of change in glucose

over time, as well as patients' insulin sensitivity) are preferred in the critical care setting.

Less evidence with regard to the effectiveness and safety of insulin protocols exists in patients with acute MI. However, data from the Mid America Heart Institute show that insulin protocols can be adapted easily to the acute MI patient population with few modifications.[55] Specifically, a modification of the Yale protocol[56] reduced mean 24-hour glucose in initially hyperglycemic patients treated with the protocol as compared with similar patients prior to protocol implementation (135 vs 181 mg/dL; $P < .001$). The rate of severe hypoglycemia was low. Similarly, this protocol targeting glucose levels between 90 and 117 mg/dL was piloted in STEMI patients for the REsearching Coronary REduction by Appropriately Targeting Euglycemia (RECREATE) trial.[55] In this setting, the mean glucose level was 117 vs 143 mg/dL in the protocol vs standard groups, respectively, after 24 hours, with differences in glucose levels maintained at 72 hours and 30 days. Although hypoglycemia occurred in 22.7% of the insulin group versus 4.4% of the standard group, there were no differences in symptomatic hypoglycemia or clinical outcomes between the groups. These results suggest that the use of evidence-based, effective, and safe protocols is preferable when clinicians decide glucose lowering is desirable with insulin infusion. Several such protocols (including the Yale protocol) are freely available in the public domain.

Although the insulin protocols can be judged based on their efficacy (adequacy of glucose control) and safety (hypoglycemia rates), they have not been tested with respect to cardiovascular endpoints. Therefore, evidence from cardiovascular outcomes trials using these approaches is needed to determine whether targeted glucose lowering improves patient outcomes.

## Conclusions

Recommendations from expert groups for the treatment of hyperglycemia along with the available data point to a gap in knowledge with respect to best glucose control practices during acute MI. There are currently no evidence-based targets for glucose management during acute MI. It also remains unclear whether management of glucose during acute MI should differ for those patients with and without preexisting diabetes.

Until more information becomes available, several suggestions are reasonable with regard to glucose management during ACS. First, assessment of glucose values during admission and throughout hospitalization provides prognostic information and, therefore, may be useful regardless of whether treatment is being considered. Second, both severe hyperglycemia and hypoglycemia should be avoided. If glucose control is being considered, evidence-based protocols that use conservative

### MAIN POINTS

- Patients with diabetes mellitus are at increased risk for coronary artery disease and have worse in-hospital outcomes following an acute coronary event when compared with nondiabetic patients. Extensive literature now documents that hyperglycemia at the time of admission for acute myocardial infarction (MI) is associated with higher in-hospital mortality.
- Hyperglycemia during an acute coronary event, whether resulting from the stress response, preexisting or new disorders of glucose metabolism, appears to be harmful to the myocardium. Given that glucose disorders both arise from and contribute to myocardial damage, the exact effects of glucose lowering on outcomes following MI are difficult to predict.
- Several randomized clinical trials have investigated the role of management of glucose disorders during an ACS. One strategy is to focus on targeted glucose control with insulin during acute MI. The data on the effect of this strategy are inconclusive. Another approach is to treat patients with the provision of glucose, insulin, and potassium at a fixed dose with the primary goal of shifting metabolism toward glucose utilization and away from fatty acid oxidation. This approach does not appear to lead to improved outcomes.
- If glucose control is being considered, evidence-based protocols that use conservative treatment thresholds and glucose targets should be used, as overly aggressive glucose control (especially targeting $< 110$ mg/dL) is unlikely to benefit patients, and may cause harm.

treatment thresholds and glucose targets should be used, as overly aggressive glucose control (especially targeting < 110 mg/dL) is unlikely to benefit patients, and may cause harm. Finally, pursuit of large clinical trials to evaluate clinical effectiveness and safety of targeted glucose control in acute MI is critically important so that more evidence-based recommendations can be provided to clinicians in the future. ■

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