

Cardiol

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**Insulin, Glucose, and Acute Coronary Syndromes:
A spoonful of medicine helps the sugar go down**

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This is to acknowledge that Darren K. McGuire, MD, MHSc has disclosed relationships with commercial concerns related directly to this program. Dr. McGuire will be discussing off-label uses in his presentation.

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Introduction

The observation that elevated glucose occurs commonly in patients hospitalized with acute coronary syndromes (ACS) was first made decades ago.¹ Since then, a multitude of studies have documented that hyperglycemia is common, affects patients with and without established diabetes, and is associated with adverse outcomes, with a graded increase in the risk of mortality and complications across the spectrum of glucose elevations observed.²⁻⁶ 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 elevation myocardial infarction, and ST-elevation myocardial infarction) can improve survival and other clinical complications, and if so, what the optimal targets, therapeutic strategies, and timing for such interventions should be during ACS.

In this presentation, I will review what is presently known 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

There is currently no uniform definition of what constitutes hyperglycemia in the setting of ACS. Prior studies used various hyperglycemia cutpoints, ranging from ≥ 110 mg/dL to ≥ 200 mg/dL.² This is compounded by different timing of glucose level assessments in this context. Most prior studies defined hyperglycemia based on the first available (or “on-arrival”) glucose value,^{2-3, 6-14} while others used fasting glucose,¹⁵⁻²⁰ as well as glucose values averaged over a period of time, such as the first 24 hours,²¹⁻²³ or the entire duration of hospitalization.⁴ 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.⁵ This recommendation is based, in part, on epidemiologic studies demonstrating that admission, mean 24-hour and mean hospitalization glucose levels above ~ 120 - 140 mg/dL are associated with increased short-term mortality risk;^{3-4, 6, 21-22} and that decline in glucose levels below ~ 140 mg/dL during ACS hospitalization is associated with better survival,²⁴ though no cause-and-effect conclusions can be drawn from these data due to their observational nature.

However, the nature of the relationship between glucose levels and short-term mortality differs in patients with and without diabetes, with a paradoxically greater magnitude of association in those without versus those with prevalent diabetes.^{3-4, 12-13, 15, 24} The risk of mortality gradually rises when glucose levels exceed ~ 110 - 120 mg/dL in patients without diabetes, while in patients with established diabetes this risk does not increase substantially until glucose levels exceed ~ 200 mg/dL.³⁻⁴ Thus, different thresholds may be appropriate to define hyperglycemia depending on the presence or absence of known diabetes.

Prevalence of elevated glucose levels in ACS

Numerous studies have documented that elevated glucose occurs commonly in patients hospitalized with ACS.²⁻⁶ While the definition of hyperglycemia varies across studies, the largest investigations show that the prevalence of elevated glucose levels (>140 mg/dL) at the time of hospital admission varies between 51-58%, affecting more than 3/4 of patients with previously diagnosed diabetes and more than 1 in 4 without prior diabetes (Figure 1).^{3-4,6} While glucose levels normalize in some ACS patients following admission (either spontaneously or due to targeted pharmacologic interventions),²⁵ the prevalence of persistent hyperglycemia remains greater than 40% throughout the course of hospitalization; and the

prevalence of severe, sustained hyperglycemia (average hospitalization glucose >200 mg/dL) is around 14%.^{4,6}

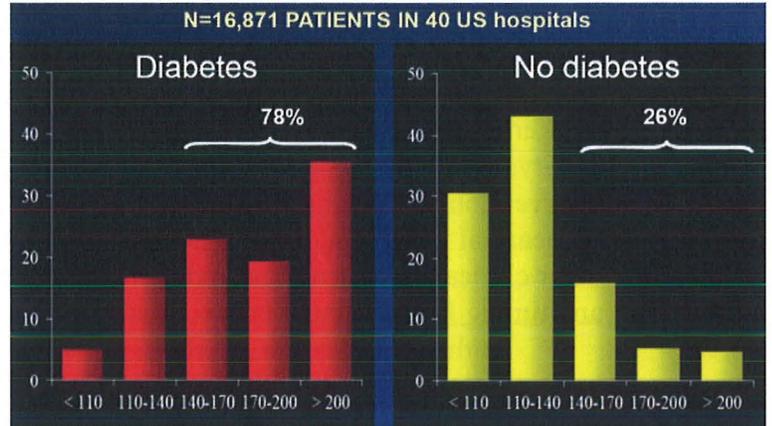


Figure 1: Distribution of "on-arrival" glucose values in patients hospitalized with AMI among those with and without prevalent diabetes. (from Kosiborod et al., *Circulation* 2008; 117:1018-1027)

The 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.²⁻⁶ The largest observational study to date to address this issue used the data from Cooperative Cardiovascular Project, and showed a near-linear relationship between higher admission glucose and greater risk of mortality at 30 days and at 1 year in over 140,000 patients hospitalized with AMI (Figure 2).³

The association between higher glucose and greater mortality risk has been established across various glucose metrics,^{2-6,26} across the spectrum of acute coronary syndromes,⁶⁻⁷ and applies to both short- and longer-term outcomes.³⁻⁴

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.³⁻⁴ Regardless of the glucose metrics used, the mortality risk starts rising at considerably lower glucose levels, and increases at much steeper slope in patients without known

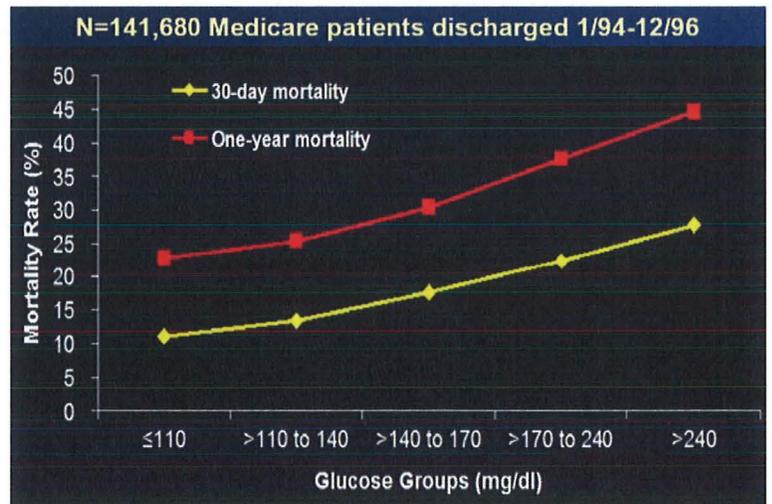


Figure 2: The relationship between admission glucose and mortality. (from Kosiborod et al., *Circulation* 2005;111:3078-86.)

diabetes, as compared with those who have previously diagnosed diabetes. The association between hyperglycemia and adverse outcomes among patients with ACS independent of diabetes status has been quantitatively summarized based on data from a large series of relatively small human studies collected over a period of three decades by Capes *et al.*² This systematic overview demonstrated that among ACS patients without known diabetes, 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 [CI] 2.9-5.4). Among ACS patients with established diabetes, those with initial glucose ≥ 180 mg/dL had a 70% increase in the relative risk of in-hospital mortality, as compared with normoglycemic patients.

More recent studies confirmed these findings and extended them across the broader range of ACS to include ST-elevation MI, non-ST 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 (Figure 3).^{6-7, 12-13} A similar relationship between elevated glucose and increased risk of death was also shown with other glucose metrics, such as post-admission fasting glucose,^{15, 18-20} and with outcomes other than mortality, including such intermediates associated with adverse clinical outcomes as “no-reflow phenomenon” following percutaneous coronary intervention (PCI),²⁷ greater infarct size;³⁻⁴ worse left ventricular systolic function;⁹ and acute kidney injury.

This phenomenon of steeper graded association between hyperglycemia and adverse outcomes in non-diabetic compared with diabetic patients is incompletely understood, and several possible explanations have been proposed. Many patients presenting with hyperglycemia in the absence of previously diagnosed diabetes actually have diabetes that simply has not been recognized or treated prior to hospitalization,²⁸ representing a higher-risk cohort since other undiagnosed and untreated cardiovascular risk factors may be more prevalent in this group of patients. Moreover, while the effect of targeted glucose control and insulin therapy in this clinical setting remains uncertain, in the absence of an existing diagnosis of diabetes, non-diabetic ACS patients with hyperglycemia are less likely to be treated with insulin than those with established diabetes, even when glucose levels are markedly elevated.³ Further contributing to this consistent observation is the fact that patients with established diabetes 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

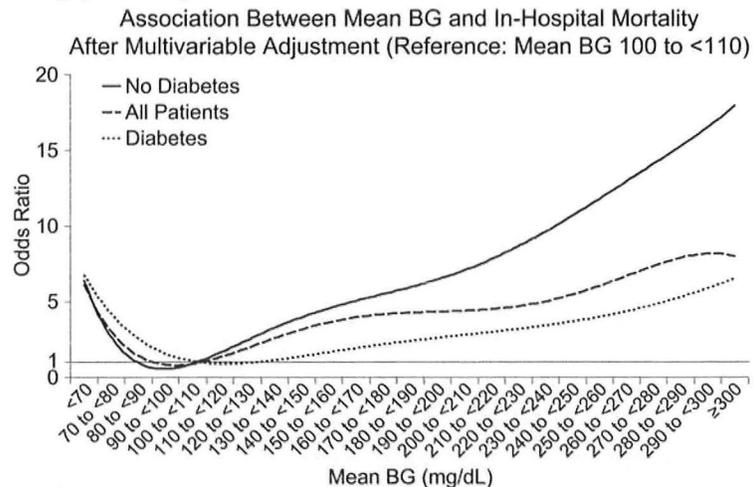


Figure 3: The association between average glucose values and risk of in-hospital mortality, overall and by diabetes status. (from Kosiborod *et al.*, *Circulation* 2008;117:1018-1027)

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 compared with those with established diabetes.

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 vs. 0.62, $p < 0.0001$).⁴ There was a significant, gradual increase in the risk of in-hospital mortality with rising mean hospitalization glucose levels. Observational sub-analyses 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.^{21, 23}

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 INfarct 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-elevation myocardial infarction, 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.²⁴ Similarly, in a study of nearly 8,000 patients hospitalized with ACS in the United States who had hyperglycemia on arrival, glucose normalization following admission was associated with better patient survival, even after adjusting for confounders (Figure 4).²⁵

Interestingly, improved survival was observed regardless of whether glucose normalization occurred as the result of insulin therapy, or happened spontaneously (without any glucose-lowering interventions). In fact, it was glucose normalization, and not insulin therapy *per se*, that was associated with better outcomes. From these observational analyses, it remains unclear whether normalization of glucose levels during hospitalization simply identifies a lower-risk group of patients, reflects differences in patient care, or whether observed improvement in survival is attributable in whole or in part to the lower glucose values observed.

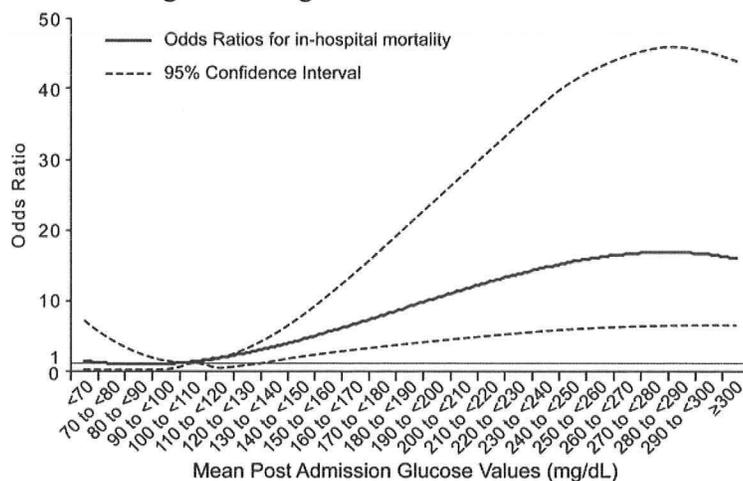


Figure 4: Glucose normalization and survival during AMI hospitalization. (from Kosiborod M et al., *Arch Intern Med.* 2009 Mar 9;169(5):438-46.)

Pathophysiologic considerations of hyperglycemia and insulin resistance in ACS

The myocardium preferentially metabolizes free fatty acids under physiologic conditions,²⁹ but can switch to metabolism of a variety of substrates during periods of stress such as ischemia, principal among them involving a switch to glucose metabolism. Countering the metabolic switch to glucose metabolism, the myocardium develops a relative insulin resistance during ischemia, underpinning extensive research into metabolic modulation of the ischemic myocardium, primarily with insulin as the focus of investigation.²⁶

Plausible pathophysiologic underpinnings potentially contributing to the incremental CVD risk observed among patients with diabetes suffering ACS events

derive from a plethora of *ex vivo*, animal and human studies, which show that hyperglycemia per se and insulin resistance of the ischemic myocardium 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 (summarized in Figure 5).^{5, 30-}

³¹ Much of the basic and translational research with

regard to the potential utility of insulin and glucose control in the setting of ACS has been based on evaluation of effects of such strategies on many of these intermediates of CVD risk in *ex vivo* studies and in animal models of ischemia and infarction.^{29-30, 32}

The pathobiologic attribution of hyperglycemia *per se* to CVD risk after ACS events remains poorly understood, but given the clear associations between severity of hyperglycemia and CVD risk in both type 1 and type 2 diabetes sharing hyperglycemia as the common pathophysiologic disturbance, hyperglycemia likely directly contributes to adverse risk observed in the setting of diabetes.³³ Among the principal vascular perturbations linked to hyperglycemia are endothelial dysfunction, vascular effects of advanced glycation end-products, adverse effects of circulating free fatty acids, and increased systemic inflammation with aberrant leukocyte-endothelial interactions, among others.³³⁻³⁵

Endothelial dysfunction is a hallmark of diabetic vascular disease,³⁶ associated with increased hypertension and adverse CVD outcomes. The mechanisms contributing to endothelial dysfunction are myriad, including abnormal nitric oxide biology, increased endothelin and angiotensin II and reduced prostacyclin activity, all contributing to abnormal control of blood flow. In the setting of ACS events, no-reflow following percutaneous intervention reflecting acute endothelial dysfunction occurs more commonly in the presence of diabetes and/or hyperglycemia and may contribute to

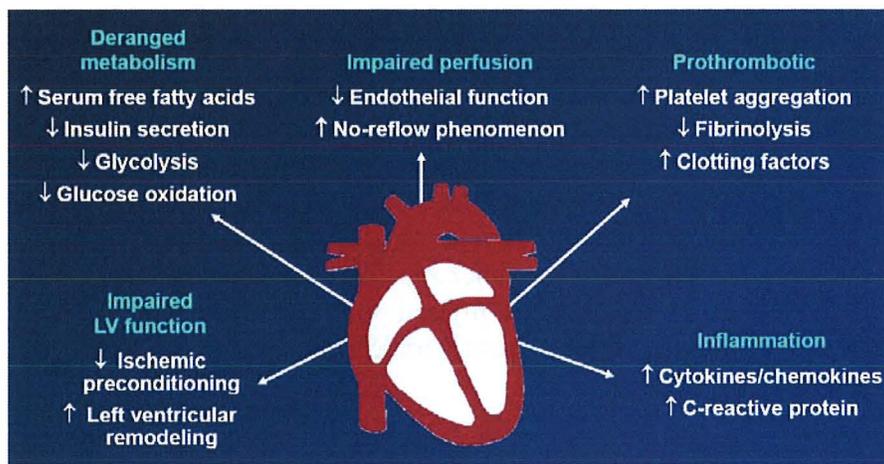


Figure 5. Summary of postulated pathophysiologic cardiovascular effects of hyperglycemia and insulin resistance in the setting of ACS events

increased myocardial jeopardy resulting in larger infarcts, increased arrhythmia, and worse systolic function.

A number of perturbations in the proteo-fibrinolytic system and platelet biology further compound the direct vascular effects of diabetes, yielding a constitutive pro-thrombotic milieu.³⁷ These abnormalities include increased circulating tissue factor, factor VII, von Willebrand factor, and plasminogen activator inhibitor 1 with decreased levels of antithrombin III and protein C. In addition, disturbances of platelet activation, aggregation, morphology, and lifespan have been well-described, further contributing to increased thrombotic potential as well as acceleration of atherosclerosis.

Increased systemic inflammation is associated with increased risk for diabetes and diabetic atherosclerotic disease risk,³⁸ with diabetes associated with increased oxidative stress and the accumulation of pro-inflammatory advanced glycation end-products. For example, diabetes is associated with lipid-rich atherosclerotic plaque with increased inflammatory cell infiltration, increased expression of tissue factor, and increased expression of the receptor for advanced glycation end products yielding a more vulnerable plaque, observed in both coronary and carotid plaque.^{33, 39}

In summary, many complex mechanistic theories have been advanced with regard to diabetic atherosclerosis. These considerations have yielded an avid investigative field and have provided myriad potential therapeutic targets for which drug development programs are presently underway.

Clinical trials in ACS: Glucose-Insulin-Potassium therapy

The use of insulin for ACS was first described in 1963 by Sodi-Pallares with the intention of facilitating potassium flux in the ischemic myocardium, so-called “polarizing therapy.” Following decades of investigation, this combination of glucose, insulin, and potassium has become known as “GIK” therapy and the focus of attention has shifted from the polarizing effects to the direct effects of insulin, including promotion of myocardial glucose oxidation, reduction of circulating non-esterified free fatty acids (FFA), improved coagulation parameters, and anti-inflammatory effects, as summarized in Figure 6.⁴⁰

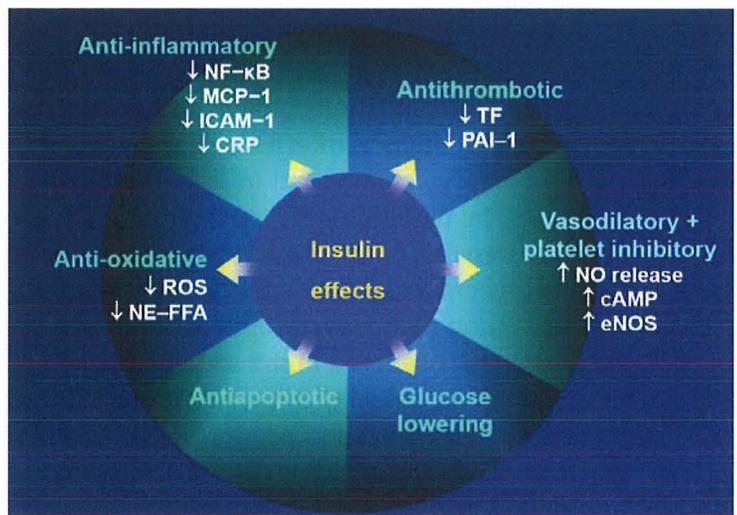


Figure 6. Effects of insulin postulated to be beneficial in the setting of ACS.

Virtually all data to date with regard to insulin treatment in the setting of ACS derive from trials evaluating the effects of GIK therapy (i.e. hyperinsulinemic, hyperglycemic therapy), as summarized in published quantitative analyses,⁴¹ and have little to do with target-driven glucose control. Studies like the Glucose-Insulin-Potassium (GIPS) trial in patients with ST elevation undergoing primary percutaneous coronary intervention,⁴² or the much larger Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation - Estudios Cardiológicos Latinoamérica (CREATE-ECLA)⁴³ and the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)-6 trials (which in total randomized nearly 23,000 participants)^{22,44} assigned patients to fixed-dose GIK infusion regardless of their initial glucose values or diabetes status, and did not pre-specify targets for glucose control. In these studies, as dictated by the infusion protocols, high-dose delivery of insulin was supported by IV glucose administration to affect modest hyperglycemia, defined by protocol as a range of 126-198mg/dL.

For example, in the (CREATE-ECLA) trial that enrolled over 20,000 patients with acute MI and demonstrated no discernible treatment benefit with GIK therapy (Figure 7),⁴³ 6-hour post-randomization glucose values were significantly higher in the GIK group than in the control group

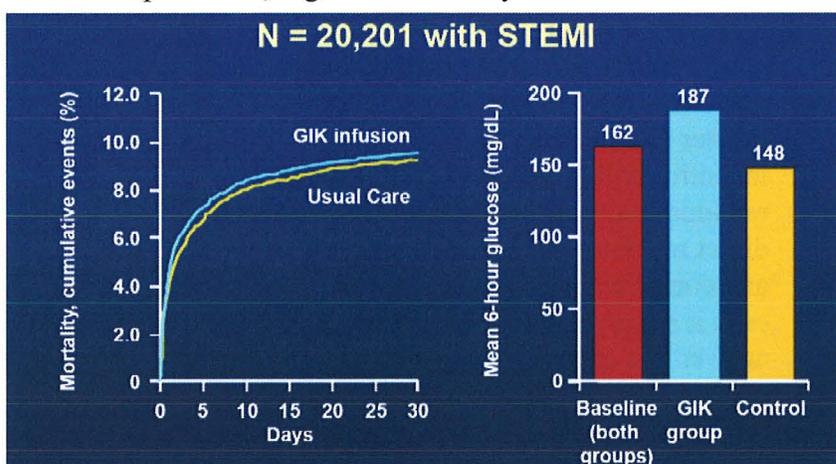


Figure 7. Mortality results and glucose levels achieved by study treatment assignment in the CREATE-ECLA trial. (from Mehta SR, et al. JAMA 2005;293:437-46.)

(187 vs. 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 the decisions about glucose management in ACS.

The Poland Glucose-Insulin-Potassium (Pol-GIK) trial randomized 954 patients with acute MI to either to fixed “low-dose GIK”, which included a much lower rate of insulin infusion (0.8-1.3 units/hour) than typical GIK regimens, versus normal saline infusion.⁴⁵ While not a typical “GIK” trial, in so far as using 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 units/hour. Second, and similar to other GIK studies, no glucose goals were pre-specified 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 the result, there was no significant difference in glucose levels 24 hours post-randomization (106 mg/dL in GIK vs. 112 mg/dL in the control arm). The study was stopped prematurely due to excess mortality in the GIK arm at 35 days (8.9%

vs. 4.8% in the control arm, $P=0.01$; Figure 8). However, due to the serious limitations of interpretation stemming from the intent of the trial to evaluate the effect of fixed-dose administration of insulin rather than targeted glucose control hypothesis, no valuable lessons can be learned about glucose-lowering and patient outcomes in AMI based on its results.

Clinical Trials in ACS: Targeted Glucose Control

While the strong relationship between elevated glucose levels and greater risk of death in ACS is incontrovertible, one 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. Since 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 glucose-insulin-potassium therapy that used a hyperinsulinemic, hyperglycemic infusion strategy, as well as data from studies of targeted glucose control conducted in non-ACS clinical settings.

Due to 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:

1. The presence of hyperglycemia at the time of patient randomization, with or without an antecedent diabetes diagnosis, since 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 post-randomization
4. The assessment of treatment effects on meaningful patient outcomes, as opposed to intermediate endpoints.

To date, no ACS trial has rigorously fulfilled all of these criteria. Trials fulfilling some but not all of these criteria are summarized in the Table 1, and will be discussed.

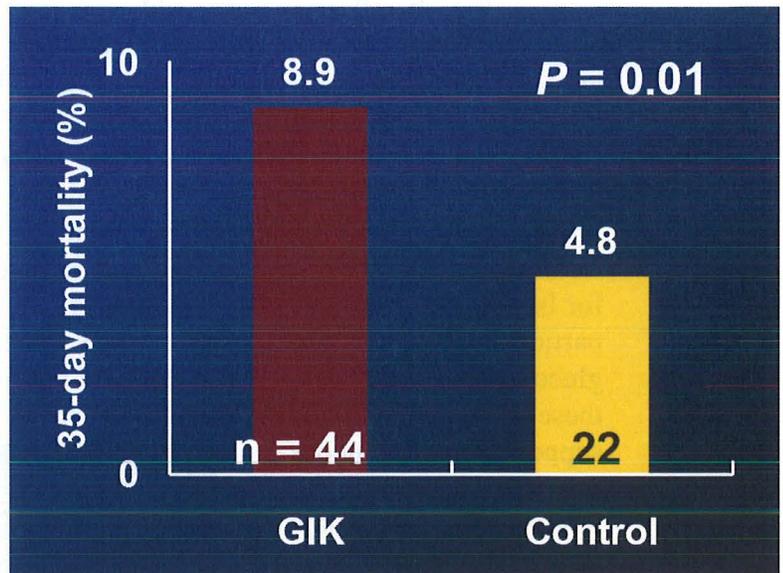


Figure 8. Mortality results from the Pol-GIK trial. (from Ceremuzynski L, et al. *Cardiovasc Drugs Ther* 1999;13:191-200.)

Table 1: Clinical Trials of Glucose Control in ACS*

Trial	Targeted Glucose Control	Elevated BG on Entry	Glucose Targets Specified	BG Contrast Achieved	Clinical Endpoints	Results
DIGAMI (1995)³⁰	+/-	+ ≈280 mg/dL	+ 126-180 mg/dL vs. usual care acutely, 90-126 mg/dL fasting BG vs. usual care afterward	+/- 173 vs. 211 mg/dL during first 24 hrs; difference in A ₁ C but not fasting BG afterward	+	+/- Mortality neutral at 3 months (primary endpoint), improved survival in glucose control arm by 1 year
Pol-GIK (1999)³⁸	-	- 124 mg/dL	-	N/A 106 vs. 112 mg/dL in intervention vs. control arms	+	Significantly higher mortality in intervention vs. control arm at 35 days
DIGAMI2 (2005)³³	+/-	+ 229 mg/dL	+ 126-180 mg/dL in-hospital vs. usual care acutely, 90-126 mg/dL fasting BG (group 1 only) vs. usual care afterward	+/- 164 vs. 180 mg/dL at 24 hrs., no difference afterward	+	- Mortality neutral between three groups
CREATE-ECLA (2005)³⁶	-	+ 162 mg/dL	-	N/A Glucose higher in intervention arm vs. control (187 vs. 148 mg/dL)	+	Mortality neutral
HI-5 (2006)²¹	+/-	+ ≈198 mg/dL	+ 72-180 mg/dL vs. usual care	- 149 vs. 162 mg/dL (P=NS) during first 24 hrs.	+	- Mortality neutral in-hospital, at 3 and 6 months

* Full clinical trials names represented by acronyms are as follows: DIGAMI - Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction, HI-5: The Hyperglycemia: Intensive Insulin Infusion in Infarction, CREATE-ECLA: Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation - Estudios Clinicos Latino America.

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.⁴⁶⁻⁴⁷ In DIGAMI, patients presenting within 24 hours of acute MI symptoms with diabetes or initial glucose levels exceeding 198 mg/dl (11 mmol/L) were randomized to an acute and chronic insulin treatment regime vs. usual care. Those randomized to the insulin arm received ≥ 24 hours of intravenous dextrose-insulin infusion titrated to maintain glucose levels of 126-180 mg/dL, initiated at 5 units/hr of IV insulin in D₅W, followed by subcutaneous insulin injections 3 times daily for the subsequent 3 months titrated to standard therapeutic targets for glucose control, to be compared with usual care. The trial enrolled 620 patients, 80% of whom had previously diagnosed diabetes. Admission glucose at study entry was 277mg/dl in the intervention group vs. 283 mg/dL in the control group. By 24 hours, those randomized to the insulin arm achieved significantly lower glucose levels compared with the control arm (173 vs. 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 vs. 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, HbA_{1c} levels were significantly lower in the intervention vs. control group at 3 months (7.0 vs. 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 in 10% of participants, resulted in discontinuation of the protocol treatment. For the primary endpoint of all-cause mortality at 3 months, there was no

significant difference between the randomized groups (38 vs. 49 deaths), with the respective p-value reported as “not significant”.⁴⁶ Therefore, from a “purist” perspective, based on failure to achieve statistical significance in the primary endpoint, 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 (Figure 9).^{46, 48} 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: a) the effects of the acute dextrose-insulin infusion; or b) the effects of multi-dose insulin injection in the outpatient setting. Therefore, while

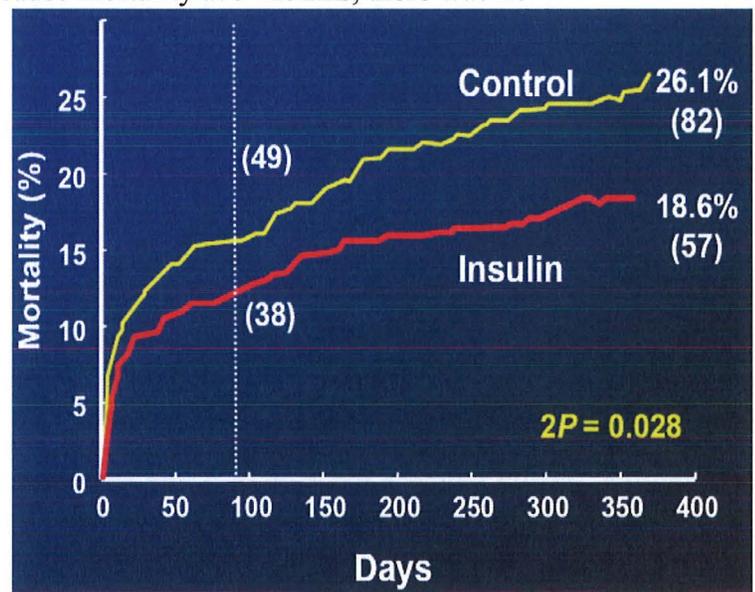


Figure 9. 1-year mortality outcomes in the DIGAMI trial. (from Malmberg K, et al. J Am Coll Cardiol 1995;26:57-65.)

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 acute, 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.²¹ Similar to DIGAMI, the therapeutic target for the insulin arm was 72-180 mg/dL and IV dextrose was infused with the insulin (either D₅W or D₁₀W); however, the insulin dose was much lower in HI-5 at 2 units/hr (contrasted with 5 units/hour used both in DIGAMI and in most trials of “GIK” therapy).²⁶ The HI-5 trial was terminated early due to slow enrollment, and failed to achieve a statistically significant difference in glucose values between the intensive and conventional glucose groups (149 vs. 162 mg/dL, 24 hours post-randomization, p=NS). Mortality assessments at hospital discharge, 30-days, and 6-months all numerically favored usual care over targeted glucose control with insulin treatment (Figure 10), though none of these comparisons were statistically significant due to very low numbers of evaluable events (6-months: 10 vs 7 deaths; p=0.62).

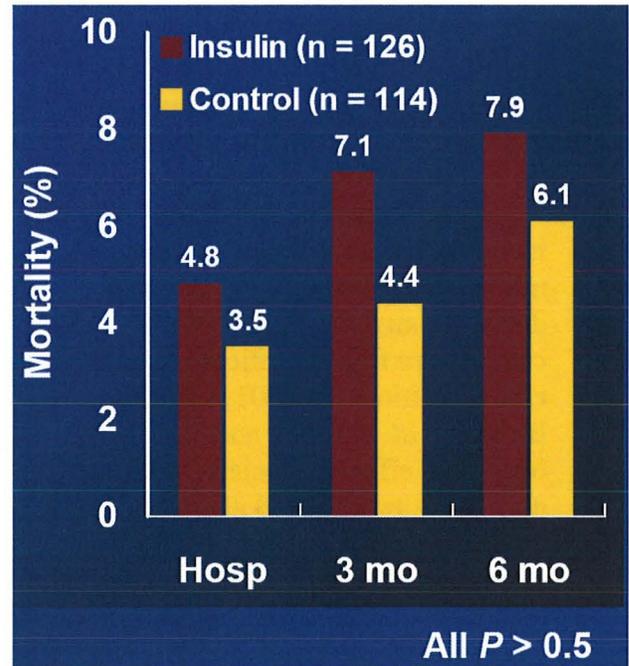


Figure 10. Mortality results observed in the Hi-5 trial. (from Cheung NW, et al. Diabetes Care 2006;29:765-70.)

The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI)-2 multi-center study attempted to determine whether potential survival benefit seen with targeted glucose control in the original DIGAMI study was primarily attributable to acute or chronic glucose lowering with insulin.⁴⁹ In DIGAMI-2, 1253 patients with acute MI and diabetes or admission glucose >198 mg/dL were randomized to one of the three subgroups: a) 24 hour insulin-glucose infusion targeting glucose of 126-180 mg/dL, followed by a subcutaneous insulin-based long-term glucose control (group 1, identical to the original DIGAMI intervention group); b) the same 24 hour insulin-glucose infusion, but followed by standard glucose control (group 2); and c) routine glucose management throughout the study period (group 3). Of note, the trial planned to recruit 3000 patients, and was stopped prematurely due to slow recruitment. Glucose levels on arrival were similar between the three arms (approximately 229 mg/dL). At 24 hours post-randomization, glucose levels were modestly lower in the two groups assigned to acute glucose lowering vs. control (164 vs. 180 mg/dL, p<0.01). This difference, while being statistically significant, was clinically small and considerably less than expected; it was also much smaller than what was observed in the original DIGAMI

study, driven primarily by more prevalent use of glucose management in the control arm compared with the original DIGAMI trial. There was no difference in either glucose or HbA₁C levels between the three groups at any other time point, with up to three years of follow up. Importantly, on average, patients in group 1 failed to achieve the targeted fasting glucose range of 90-126 mg/dL during the outpatient management phase. Mortality over 2 years was not statistically different between the three groups (23.4% vs. 21.2% and 17.9% in groups 1, 2 and 3, respectively; P=0.83 for group 1 vs. group 2; and P=0.16 for group 1 vs. group 3). Due to its limitations (primarily lack of substantial contrast in glucose levels between the three groups), the DIGAMI-2 trial did not provide a definitive answer on whether targeted glucose lowering (whether acute or chronic) has any clinical value in contemporary management of patients with AMI.

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 Berghe *et al.* reported notable beneficial effects associated with normalization of blood glucose using an insulin infusion compared with usual care among patients hospitalized in a surgical intensive care unit (Figure 11).⁵⁰ These observations fueled enthusiasm among clinicians and professional societies to endorse a strategy of targeted glucose control across critically ill hospitalized populations.⁵¹

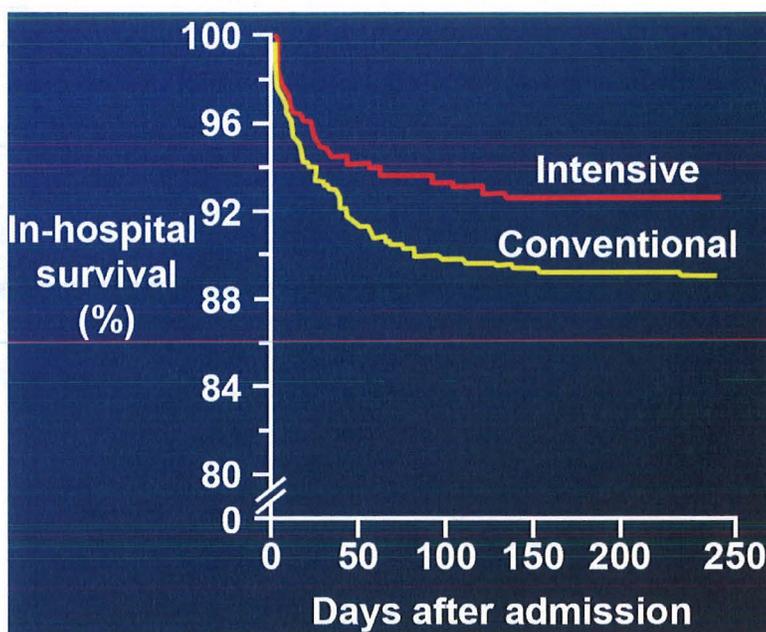


Figure 11. Effect of normalization of blood glucose among SICU patients. (from van den Berghe G, et al. N Engl J Med 2001;345:1359-67.)

However, in the 8 years that followed, several additional randomized trials in various ICU patient populations have failed to reproduce these beneficial results, summarized in Table 2.⁵²⁻⁵⁶

Table 2. Summary of randomized trials of normalization of blood glucose in various clinical cohorts.

Study	Population	Glucose target (mg/dL)	1 st endpoint	Result	Hypoglycemia
Van den Berghe-1	SICU (N = 1,548)	80 – 110 vs. 180 – 200	ICU death	42% RRR	7.2% (< 40 mg/dL)
Van den Berghe-2	MICU (N = 1,200)	80 – 110 vs. 180 – 215	Hosp. death	No Δ	18.7% (mean 32 mg/dL)
Gandhi	Cardiac surgery (N = 400)	80 – 100 vs. usual care	Death/DSWI/CVA/ vent. days/renal failure/arrhythmia	No Δ	4.9% (< 60 mg/dL)
WISEP*	MICU-sepsis (N = 488)	80 – 110 vs. 180 – 200	28-d death	\uparrow mortality trend	17.0% (< 40 mg/dL)
GIST-UK*	Stroke ICU (N = 933)	72 – 126 vs. usual care	90-d death	No Δ	15.7% (< 70 mg/dL)
European Glucontrol*	MICU (N = 1,101)	80 – 110 vs. 140 – 180	Hosp. death	\uparrow mortality Trend	8.6% (< 40 mg/dL)

* Stopped early futility / hypoglycemia

Key among these more recent trials are a) the same investigators at the same institution using the same protocol as the SICU trial, testing intensive glucose lowering in the medical ICU patients, and showing lower morbidity, but no difference in the trial primary endpoint of mortality with intensive glucose lowering vs. usual care;⁵⁶ and b) 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, and demonstrated significantly higher mortality with intensive vs. more conservative glucose control (Figure 12).⁵³

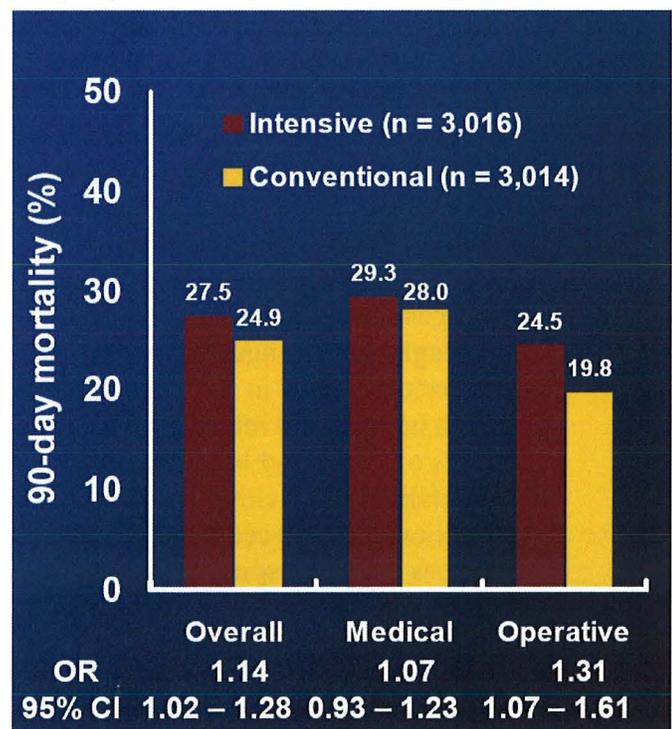


Figure 12. Mortality results from the NICE-SUGAR trial, overall and by ICU type. (from Finfer S, et al. N Engl J Med 2009;360:1283-97.)

In aggregate, these recent trial results have substantially tempered enthusiasm for aggressive glucose lowering in the ICU setting across a spectrum of clinical settings. However, the results of NICE-SUGAR should be critically interpreted in the context of the study design; NICE-SUGAR compared "very intensive" glucose control to "good" glucose control, not to "usual care". Specifically, an intravenous insulin protocol was used in more than two thirds of patients in the control arm, producing an average glucose of ≈ 142 mg/dL. This degree of glucose control is more intensive than what was achieved in control groups of other critical care studies, lower than what was achieved in the intensive arm of most ACS studies, and much lower than what is typically seen in routine clinical care. Thus, the most appropriate conclusion from NICE-SUGAR study is that "good" glucose control (with values somewhere between 140-180 mg/dL) is sufficient, and more aggressive glucose lowering provides no additive benefit and likely increases mortality.

Regardless, 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;^{3, 57} thus, it can also vary substantially between cardiac and non-cardiac disease states.

The prognostic importance of hypoglycemia in patients with ACS

Since therapy of hyperglycemia in the hospital necessitates the use of insulin, it is inevitable that glucose lowering in the in-patient setting will produce excess hypoglycemia. The risk of hypoglycemia associated with intensive glucose control in acutely ill patients remains an important concern, with the incidence of severe hypoglycemia observed in the recently reported trials as high as 19%. This may be an especially important consideration in the treatment of ACS events, where the counter-hormone response associated with hypoglycemia may be particularly deleterious in the setting of ischemic and infarcting myocardium.

Several observational studies suggest that glucose values in the hypoglycemic range may adversely impact mortality in ACS, associated with up to 2-fold increased adjusted odds of short- and long-term mortality,^{6, 58-59} with a J-shaped relationship between average glucose values during hospitalization and in-hospital mortality observed across trials (Figure 13).⁴ Whether hypoglycemia is directly harmful in patients with ACS, or whether it is

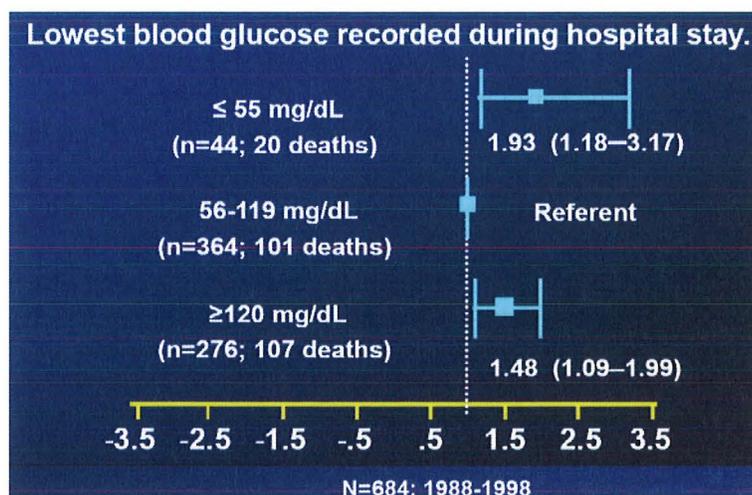


Figure 13. Adjusted association between in-hospital hypoglycemia and 2-year mortality following an ACS event. (from Svensson AM, et al. Eur Heart J 2005;26:1255-61.)

simply a marker for the most critically ill patients was recently evaluated in a large observational study.⁵⁹ In a more recent observational study, 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 (Figure 14).⁵⁹ Two subsequent analyses of data from the DIGAMI-2 and CREATE-ECLA trials also found no significant association between

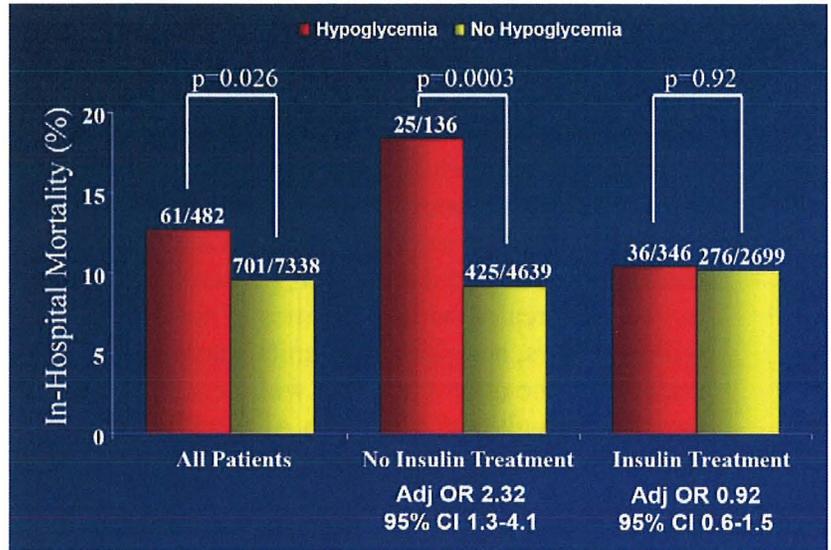


Figure 14. Association between hypoglycemia and mortality among ACS patients, overall and stratified by insulin use. (from Kosiborod M, et al. JAMA 2009;301:1556-64.)

hypoglycemia and mortality, after adjustment for confounders.^{23, 60} These findings suggest that hypoglycemia is a marker of severe illness, rather than a direct cause of adverse outcomes. While continuous efforts to avoid hypoglycemia are certainly warranted, these studies cast some doubt on the assumption that the lack of clinical benefit from intensive glycemc control in clinical trials is simply a consequence of excess hypoglycemia. In addition, it should be noted that in the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE SUGAR) trial discussed above,⁵³ the incidence of hypoglycemia associated with the insulin infusion was the lowest (6.8%) of all the trials reported to date, yet it is the only trial to demonstrate statistically significant increased mortality with intensive glycemc control in the ICU setting, raising the possibility that the adverse effects of the insulin infusion may be mediated by alternative mechanisms. The importance of this observation is that the ability to avoid excess hypoglycemia should no longer be justification for continued use of insulin infusions targeting tight glycemc control.

Current patterns of glucose control in ACS

The current practice of glucose management in hospitalized patients in the US is highly variable, largely reflecting the uncertainty driven by the accumulated data with regard to optimal strategies, targets, and patient populations.⁶¹ Large proportions of ACS patients with hyperglycemia do not receive glucose-lowering therapy, even in the setting of marked hyperglycemia (Figure 15); this is particularly

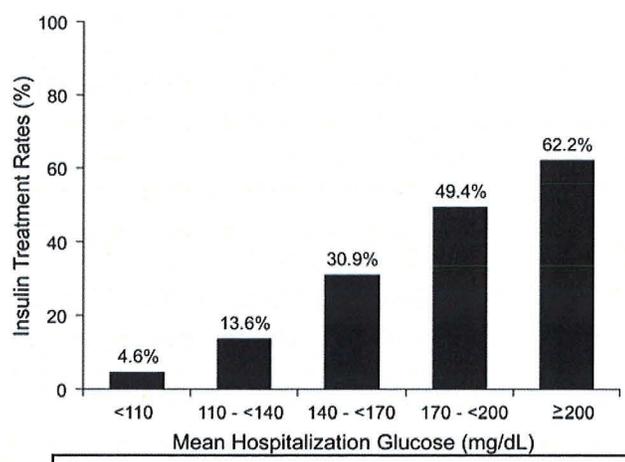


Figure 15: Insulin use in ACS patients across mean hospitalization glucose levels. (from Kosiborod M, et al. Circ 2008;117:1018-27.)

evident among those without previously diagnosed

diabetes.³ A recent study from the United Kingdom showed that 64% of patients without diabetes with admission glucose ≥ 11 mmol/L (~200 mg/dL) received no glucose-lowering treatments during hospitalization.⁶² 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. In addition, the inconsistent data in the field across trials of various populations using a variety of insulin infusion strategies and glucose targets has created wide disparities in the insulin infusion algorithms across centers, and within centers, across clinical units, summarized in Table 3.⁶¹ These observations underscore the urgent need for well-designed, large-scale clinical outcomes 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.

Table 3. Disparities in insulin infusion regimens across selected centers.

Author	Target glucose (mg/dL)	Bolus (U)	Initial infusion rate (U/h)	Insulin infused BG > 200 mg/dL (U)	Highest hourly dose (U)
Bode	100 – 150	0	8	41	11
Boord	120 – 180	0	1	14.3	4.3
Chant	90 – 144	0	6	42	15
Furnary	100 – 150	12	6.5	59.5	18.5
Goldberg	100 – 139	4.5	4.5	26	9
Kanji	80 – 110	3	3	41	12
Krinsley	< 140	0	10	40	10
Marks	120 – 180	0	1	54	18
Van den Berghe	80 – 110	0	4	40	15
Zimmerman	101 – 150	10	4	88	21

Summary and recommendations:

Until further data become available, specific recommendations with regard to glucose management in ACS remain grounded on epidemiologic observations, mechanistic hypotheses, and expert consensus, in the absence of clinical outcomes evidence. Reflecting this uncertainty, in 2008 the AHA published an update on its position regarding glucose targets for ACS/MI patients, which substantially liberalized previous recommendations.⁵ This AHA position advocates for a glucose treatment threshold of >180 mg/dl, with no therapeutic targets of control specified. A similar position was more recently advocated in the 2009 focused update of STEMI guidelines,⁶³ and also endorsed by the revised AACE/ADA guidelines – which now recommend the same glucose threshold for therapeutic intervention in critically ill patients of

>180mg/dl,⁶⁴ with suggested therapeutic target of glucose control specified at 140-180 mg/dL, a substantially more liberal approach than prior guidelines.⁵¹ While 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 regards to glucose management during ACS hospitalization:

1. Assessment of glucose values at the time of admission, and glucose monitoring during hospitalization will provide useful information in regards 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 line 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 based on existing data.
 - b. Evidence-based protocols should be used when and if glucose control strategies are implemented. Such protocols should
 - i. have demonstrated effectiveness and safety with regard to targeted glucose control in the variety of clinical settings;
 - ii. incorporate the rate of change in glucose values as well as insulin sensitivity in determination of insulin infusion rates and adjustments;
 - iii. provide specific directions on the frequency of glucose testing and hypoglycemia management.
3. Lastly, 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 regards to glucose management during ACS.

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