Differential Clinical Outcomes Associated With Hypoglycemia and Hyperglycemia in Acute Myocardial Infarction

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Background—In patients with acute myocardial infarction (AMI), hyperglycemia predicts death, but the prognostic significance of hypoglycemia is controversial.

Methods and Results—We evaluated the prognostic significance of hypoglycemia and hyperglycemia in 30 536 AMI patients in a post hoc analysis of 2 large trials of glucose-insulin-potassium therapy in AMI. Glucose levels on admission and at 6 and 24 hours after admission, as well as 30-day mortality, were documented. In separate multivariable Cox models for admission and postadmission glucose, we compared the prognostic value of hypoglycemia (≤70 mg/dL) and hyperglycemia (≥140 mg/dL) with normoglycemia (70 and <140 mg/dL). Analyses were repeated with hypoglycemia defined as glucose ≤60 mg/dL and in key subgroups based on diabetes or insulin (glucose-insulin-potassium) allocation status. Both high and low percentiles of admission glucose predicted increased 30-day mortality. However, for postadmission glucose, this U-shaped relationship was attenuated so that only high and not low glucose levels remained prognostic. Hyperglycemia (≥140 mg/dL), both on admission (adjusted hazard ratio 1.43, 95% confidence interval 1.32 to 1.56, P<0.0001) and after admission (adjusted hazard ratio 1.47, 95% confidence interval 1.31 to 1.66, P<0.0001), predicted death compared with normoglycemia. In contrast, hypoglycemia (glucose ≤70 mg/dL) on admission was not prognostic (adjusted hazard ratio 1.16, 95% confidence interval 0.84 to 1.56, P=0.37), nor was postadmission hypoglycemia (adjusted hazard ratio 0.96, 95% confidence interval 0.72 to 1.26, P=0.75). Exploratory analyses that redefined hypoglycemia as glucose ≤60 mg/dL showed consistent results, as did analyses restricted to diabetic patients (18% of the study population). Postadmission hypoglycemia was more common in insulin (glucose-insulin-potassium)–treated patients (6.9%) than in untreated patients (3.4%) but did not predict mortality in either subgroup.

Conclusions—Both admission and postadmission hyperglycemia predict 30-day death in AMI patients. In contrast, only hypoglycemia on admission predicted death, and this relationship dissipated after admission. These data suggest hypoglycemia may not be a direct mediator of adverse outcomes in AMI patients. (Circulation. 2009;120:2429-2437.)

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

Hyperglycemia is common during acute myocardial infarction (AMI). It is also a strong predictor of mortality in AMI patients with and without a history of diabetes mellitus.1–5 Recognition of the adverse outcomes associated with in-hospital hyperglycemia has prompted professional societies to advise glucose control in AMI patients.5,6 However, implementation of glucose control is often tempered by concerns of inducing hypoglycemia during AMI. Indeed, some studies have reported an association between low glucose levels and adverse outcomes in AMI patients,6,7,8 whereas other studies do not support this association.9,10 Most of these prior studies have not determined whether the risk associated with admission hypoglycemia or hyperglycemia extends to postadmission derangements in glucose levels, or they have not reported the link between hypoglycemia and adverse outcomes in key subgroups (eg, patients with and without diabetes or patients treated or untreated with insulin).

Clinical Perspective on p 2437

In 2 recent large randomized controlled trials of glucose-insulin-potassium (GIK) therapy in AMI, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction and the GIK Myocardial Infarction trial, investigators assessed the impact of GIK on patient outcomes.8,9 In both trials, patients with AMI who were randomized to the GIK group had significantly lower glucose levels than those in the control group.8,9 These data support the hypothesis that the beneficial effects of GIK therapy may be mediated by its impact on glucose levels.8,9

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Infarction Treatment and Evaluation–Estudios Clinicos Latino America (CREATE-ECLA) trial and the Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) trial. In-hospital glucose levels and mortality at 30 days were documented in 30,536 subjects. We analyzed data from these trials to (1) evaluate the association between admission hypoglycemia or hyperglycemia and mortality at 30 days in hospitalized AMI patients, (2) determine whether these relationships differ for glucose levels measured in the postadmission period, and (3) discern whether these relationships vary in important subgroups, including patients with and without diabetes and patients who did or did not receive insulin during hospitalization for AMI.

Methods

The CREATE-ECLA and OASIS-6 Trials

Patients in whom in-hospital glucose levels were documented (n=30,536)

Patients with AMI enrolled in the CREATE-ECLA and OASIS-6 trials (n=32,293)

No in-hospital glucose levels documented (n=1757)

Admission glucose documented (n=30,297)

Post-admission glucose documented (n=25,513)

Admission hypoglycemia (glucose ≤ 70) (n=459)

Admission normoglycemia (glucose > 70 and < 140) (n=15,604)

Admission hyperglycemia (glucose ≥ 140) (n=13,268)

Post-admission hypoglycemia (glucose ≤ 70) (n=1244)

Post-admission normoglycemia (glucose > 70 and < 140) (n=11,001)

Post-admission hyperglycemia (glucose ≥ 140) (n=11,504)

Analyzed for 30-day death (n=30,297); None lost to follow-up

Analyzed for 30-day death (n=25,513); None lost to follow-up

Figure 1. Patient flow chart.

Study Population, Glucose Monitoring, and Insulin Treatment

Of the 32,293 patients in the combined trial population, 30,536 (95%) had 1 or more glucose levels documented during the course of the hospitalization and were included in the present analysis (Figure 1). A history of diabetes mellitus was based on self-report. Venous blood samples were drawn, and glucose levels were measured up to 3 times within the first 24 hours of hospitalization: At hospital admission, 6 hours after admission, and 24 hours after admission. Glucose levels were measured at the local sites. Admission glucose was documented in 30,297 patients, and postadmission glucose (at 6 and/or 24 hours) was documented in 25,513 patients. Fewer patients had documented postadmission glucose levels than admission glucose levels because several sites stopped documenting postadmission glucose after termination of the GIK component of the OASIS-6 trial.

In these trials, the GIK study infusion was prepared locally and administered to patients in the insulin arm according to specific instructions so that there was uniformity in insulin treatment across sites. The solution consisted of 25% glucose, regular insulin 50 U/L, and potassium 80 mEq/L, and its administration was initiated immediately after randomization. The GIK solution was infused at a fixed rate of 1.5 mL · kg⁻¹ · h⁻¹ for 24 hours and was adjusted occasionally because of concerns about hyperkalemia and volume overload but generally not for glucose levels. There was no target glucose level given that the goal of administering fixed-dose GIK was to improve energy balance of the ischemic myocardium and not to achieve glucose control.

Definition of Glucose Groups and Study Outcomes

Patients were categorized into 1 of 3 glucose groups based on admission glucose: Hypoglycemia (admission glucose ≤ 70 mg/dL), normoglycemia (glucose >70 and <140 mg/dL), and hyperglycemia (glucose ≥ 140 mg/dL). Glucose ≤ 70 mg/dL (with or without symptoms of hypoglycemia) was used to define hypoglycemia according to the American Diabetes Association definition. Glucose ≥ 140 mg/dL was used to define hyperglycemia on the basis of a recent American Heart Association statement on hyperglycemia in acute coronary syndromes. These cut points were prespecified before the present analyses were undertaken.

Patients were similarly categorized into 3 mutually exclusive groups based on postadmission glucose levels. Because subjects could have more than 1 postadmission glucose level (at both 6 and 24 hours), postadmission hypoglycemia was defined as 1 or both postadmission glucose levels ≤ 70 mg/dL, hyperglycemia as 1 or
both glucose levels $\geq 140$ mg/dL and neither value $\leq 70$ mg/dL, and normoglycemia as both postadmission glucose values $>70$ and $<140$ mg/dL.

We sought to determine the relationship between glucose group (hypoglycemia, normoglycemia, or hyperglycemia) and clinical outcomes for admission and postadmission glucose levels. The primary end point of the CREATE-ECLA and OASIS-6 trials, 30-day all-cause death, was used as the main outcome measure of the present study. Deaths were adjudicated centrally, and vital status was ascertained in all 30 536 patients (100%) in the present study. We also repeated all analyses and models for the 30-day composite end point of death or recurrent myocardial infarction, but these data were similar to those for death alone and are therefore not presented.

### Data Analysis and Statistical Methods

The rate of 30-day death was first plotted by deciles of admission glucose, 6-hour postadmission glucose, and 24-hour postadmission glucose. To further characterize the relationship between glucose levels and mortality for very low glucose levels, the first glucose decile was further partitioned into 10 equal percentiles. In the analyses that compared outcomes among groups of admission and postadmission glucose levels (hypoglycemia, normoglycemia, and hyperglycemia), baseline characteristics and in-hospital therapies were compared across glucose groups as mean values or percentages. Thirty-day event rates were compared across glucose groups (separately for admission and postadmission glucose levels) with Cox proportional hazards models. Subjects with hyperglycemia or hypoglycemia were each compared with the reference group of normoglycemia. Separate Cox models were constructed for the 30-day outcomes of death alone and of death or reinfarction. Cox models were adjusted for age, sex, diabetes status, admission systolic blood pressure, admission heart rate, Killip class on admission, location of infarction on admission ECG (anterolateral versus other), administration of reperfusion therapy (thrombolysis and/or primary percutaneous coronary intervention versus neither), the study of enrollment (CREATE-ECLA or OASIS-6), and allocation to GIK or control. These covariates were selected because they were the strongest predictors of 30-day mortality in the Global Utilization of Streptokinase and Tissue Plasminogen Activator to Treat Occluded Arteries (GUSTO-I) trial database of $>40 000$ AMI patients.\(^\text{15}\)

Models for groups of postadmission glucose were also adjusted for admission glucose, both because admission and postadmission glucose levels were independent predictors of 30-day mortality and because prior studies have acknowledged their independent prognostic value in their analyses.\(^\text{8}\) In a sensitivity analysis, Cox models were also constructed for the overall population in which hypoglycemia was redefined as glucose $\leq 60$ mg/dL.

A statistical interaction test suggested the relationship between glucose groups and clinical outcomes differed in diabetic and nondiabetic subjects; therefore, analyses for both admission and postadmission glucose were conducted separately in diabetic and nondiabetic subjects. Similarly, owing to a statistical interaction test, in patients with hyperglycemia, results for postadmission glucose were reported separately in these groups, but not for admission glucose, because the measuring of baseline glucose preceded the allocation to GIK or no GIK.\(^\text{14}\)

SAS version 9.1 and SPSS version 14.0 were both used for statistical analysis. All statistical tests were 2-sided, and a $P$ value $<0.05$ was declared statistically significant for all analyses, except for interaction tests, for which a more liberal $P$ value of $<0.10$ was used to identify a statistical interaction so that differences between important subgroups (eg, patients with and without diabetes or patients allocated to insulin GIK or no GIK) would not be missed.

### Results

#### Study Population and Baseline Characteristics

Admission glucose was captured in 30 297 subjects (99.2%). Glucose levels at 6 and 24 hours were documented in 24 276 (79.5%) and 24 260 (79.4%) subjects, respectively, such that 1 or both of these postadmission glucose levels were documented in 25 513 subjects (83.6%; Figure 1). Table 1 shows baseline characteristics among groups of admission glucose. A total of 459 patients (1.5%) had hypoglycemia (glucose $\leq 70$ mg/dL), 15 604 (51.5%) were in the normoglycemic range (glucose $>70$ and $<140$ mg/dL), and 14 234 (47.0%) had hyperglycemia (glucose $\geq 140$ mg/dL). The mean admission glucose levels of the 3 groups were 59, 111, and 219 mg/dL, respectively. A history of diabetes was more common in individuals with hypoglycemia (7.6%) and hyperglycemia (32.9%) than in those with normoglycemia (4.4%). Subjects with admission hypoglycemia were younger, were more often male, had a lower weight, and had a slightly lower admission systolic blood pressure and admission Killip class than subjects with hyperglycemia. The use of in-hospital β-blockers was more common and the use of lipid-lowering agents or any reperfusion therapy was less common in patients with admission hypoglycemia than in the normoglycemia and hyperglycemia groups.

Table 1 also presents baseline characteristics among groups of postadmission glucose. A total of 1244 patients (4.9%) had at least 1 postadmission hypoglycemic value (glucose $\leq 70$ mg/dL), 11 001 (43.1%) had all normoglycemic values (glucose $>70$ and $<140$ mg/dL), and 13 268 (52.0%) had 1 or more hyperglycemic values (glucose $\geq 140$ mg/dL and no glucose levels $\leq 70$ mg/dL). Among subjects with postadmission hypoglycemia, normoglycemia, and hyperglycemia, the mean admission glucose levels were 126, 126, and 193 mg/dL, respectively (Table 1). The corresponding mean glucose levels at 6 hours were 101, 110, and 213 mg/dL, and the mean glucose levels at 24 hours were 79, 107, and 177 mg/dL (Table 1). Patterns of baseline characteristics across groups of postadmission glucose were similar to those seen for admission glucose.

#### Relationship Between Glucose Deciles and 30-Day Mortality

The risk of 30-day death increased with increasing admission glucose levels in the overall population, particularly starting with the 6th glucose decile (glucose level $\approx 140$ mg/dL or higher; Figure 2, top). When the first admission glucose decile was partitioned into 10 equal percentiles, a trend toward higher mortality was demonstrated in patients with very low glucose levels (Figure 2, top), particularly for glucose $\leq 60$ mg/dL, although the confidence intervals (CIs) were wide. This U-shaped relationship between glucose levels and mortality became attenuated at 6 hours after admission (Figure 2, middle) and even more attenuated at 24 hours after admission (Figure 2, bottom), such that there was still a clinically and statistically significant association between 24-hour glucose and mortality at the highest glucose deciles but a much weaker association that was no longer statistically significant (overlapping CIs) at the lowest glucose percentiles (Figure 2, bottom).

#### Hypoglycemia, Hyperglycemia, and Risk of 30-Day Death in the Overall Population

**Admission Glucose**

Of the 30 297 subjects with admission glucose, 2793 (9.2%) died by 30 days. The rate of 30-day death was 12.3% in
subjects with admission hyperglycemia, 8.7% in those with hypoglycemia (glucose ≥70 mg/dL), and 6.4% in those with normoglycemia (Table 2). Admission hyperglycemia predicted a greater risk of death than normoglycemia in both unadjusted (hazard ratio [HR] 1.97, 95% CI 1.82 to 2.13, \(P<0.0001\)) and adjusted (HR 1.43, 95% CI 1.32 to 1.56, \(P<0.0001\)) analyses. In contrast, hypoglycemia on admission was associated with increased mortality compared with normoglycemia in unadjusted analysis (HR 1.37, 95% CI 1.00 to 1.88, \(P=0.0494\)), but the risk dissipated and was no longer statistically significant after multivariable adjustment (HR 1.16, 95% CI 0.84 to 1.62, \(P=0.37\)).

**Postadmission Glucose**

Of the 25,513 subjects with postadmission glucose levels, 1769 (6.9%) died by 30 days (Table 3). The risk of death was higher among subjects with postadmission hyperglycemia (9.0%) than among those with normoglycemia (4.7%) in both unadjusted (HR 1.95, 95% CI 1.75 to 2.16, \(P<0.0001\)) and adjusted (HR 1.47, 95% CI 1.31 to 1.66, \(P<0.0001\)) analyses. In contrast, the risk of death in patients with postadmission glucose ≥70 mg/dL was no different from the risk in normoglycemic patients (4.7% versus 4.7%) as described in the text.

**Sensitivity Analyses**

Sensitivity analyses in which hypoglycemia was defined as glucose ≥60 mg/dL demonstrated a higher rate of death in patients with hypoglycemia than in those with normoglycemia on admission (Table 2), although the CIs were wide and the results not quite statistically significant (adjusted HR 1.50, 95% CI 0.95 to 2.37, \(P=0.079\)). This association was attenuated in the postadmission period such that a glucose level ≥60 mg/dL did not predict death (adjusted HR 1.21, 95% CI 0.84 to 1.75, \(P=0.30\); Table 3).

**Glycemic Status and Risk of Mortality by Diabetes History**

Of the 30,536 subjects included in these analyses, 5440 (17.8%) had a history of diabetes. In the association between these two variables, adjustment for confounders was limited by small numbers in the normoglycemic and hypoglycemic groups, but the results were not statistically significant. Subjects in both groups with diabetes had a higher risk of death than those without diabetes (HR 1.77, 95% CI 1.63 to 1.92, \(P<0.0001\)) and (HR 1.39, 95% CI 1.23 to 1.57, \(P<0.0001\)) for normoglycemia and hypoglycemia, respectively.
postadmission glucose and 30-day death, there was a statistical interaction with diabetes history ($P=0.038$). Therefore, the risk of death by glycemic group was reported separately in patients with and without diabetes mellitus for both admission glucose (Table 4) and postadmission glucose (Table 5). In nondiabetic subjects, 30-day death was associated with admission hyperglycemia (adjusted HR 1.43, 95% CI 1.30 to 1.56, $P<0.0001$) but not admission hypoglycemia (adjusted HR 1.04, 95% CI 0.72 to 1.50, $P=0.85$; Table 4). Findings were consistent in nondiabetic patients when postadmission glucose was considered (Table 5). In contrast, in diabetic subjects, both hyperglycemia on admission (adjusted

Table 2. Outcomes at 30 Days by Group of Admission Glucose in the Overall Population

<table>
<thead>
<tr>
<th>Hypoglycemia $\leq 70$ mg/dL; normoglycemia $&gt;70$ but $&lt;140$ mg/dL; hyperglycemia $\geq 140$ mg/dL</th>
<th>No. of Patients</th>
<th>Death at 30 d, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>459</td>
<td>40 (8.7)</td>
<td>1.37 (1.00–1.88)</td>
<td>1.16 (0.84–1.62)</td>
<td>0.37</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>15 604</td>
<td>1004 (6.4)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14 234</td>
<td>1749 (12.3)</td>
<td>1.97 (1.82–2.13)</td>
<td>1.43 (1.32–1.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypoglycemia $\leq 60$ mg/dL; normoglycemia $&gt;60$ but $&lt;140$ mg/dL; hyperglycemia $\geq 140$ mg/dL</td>
<td>173</td>
<td>19 (11.0)</td>
<td>1.74 (1.10–2.73)</td>
<td>1.50 (0.95–2.37)</td>
<td>0.079</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>15 890</td>
<td>1025 (6.5)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14 234</td>
<td>1749 (12.3)</td>
<td>1.97 (1.82–2.12)</td>
<td>1.44 (1.32–1.56)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hypoglycemia, normoglycemia, and hyperglycemia were defined as glucose $\leq 70$, $>70$ but $<140$, and $\geq 140$ mg/dL, respectively. Analyses were repeated with hypoglycemia defined as $<60$ mg/dL. Models were adjusted for age, sex, systolic blood pressure, heart rate, Killip class, location of infarction on admission ECG, administration of reperfusion therapy, study of enrollment (CREATE-ECLA or OASIS-6), GIK allocation, and diabetes mellitus.
we found that hypoglycemia (glucose < 70 mg/dL) among those who were not (6396/14,535 [43.0%]) received insulin (GIK) therapy and 14,535 (62.6%) as among those who were not (490/14,535 = 3.4%), which suggests that many of the hypoglycemic episodes in the GIK arm were insulin induced and not spontaneously occurring. Even though postadmission hypoglycemia was more common in GIK-treated than in non-GIK-treated patients, it was not associated with increased mortality in either insulin (GIK)-treated patients (adjusted HR 0.85, 95% CI 0.59 to 1.24, P = 0.41) or untreated patients (adjusted HR 1.02, 95% CI 0.67 to 1.56, P = 0.92) compared with normoglycemic patients (Table 6).

### Table 3: Death at 30 Days by Group of Postadmission Glucose in the Overall Population

<table>
<thead>
<tr>
<th>Glucose Status</th>
<th>No. of Patients</th>
<th>Death at 30 d, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia ≤ 70 mg/dL; normoglycemia &gt; 70 but &lt; 140 mg/dL</td>
<td>1244</td>
<td>59 (4.7)</td>
<td>1.00 (0.77–1.31)</td>
<td>0.96 (0.72–1.26)</td>
<td>0.75</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>11,001</td>
<td>519 (4.7)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13,268</td>
<td>1,191 (9.0)</td>
<td>1.95 (1.75–2.16)</td>
<td>1.47 (1.31–1.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypoglycemia ≥ 60 mg/dL; normoglycemia &gt; 60 but &lt; 140 mg/dL</td>
<td>542</td>
<td>32 (5.9)</td>
<td>1.26 (0.89–1.81)</td>
<td>1.21 (0.84–1.75)</td>
<td>0.30</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>11,548</td>
<td>540 (4.7)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13,423</td>
<td>1,197 (8.9)</td>
<td>1.95 (1.76–2.16)</td>
<td>1.47 (1.31–1.65)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hypoglycemia was defined as either 6- or 24-hour glucose ≤ 70 mg/dL; normoglycemia as both postadmission glucose levels > 70 but < 140 mg/dL, and hyperglycemia as at least 1 postadmission glucose ≥ 140 mg/dL and neither value ≤ 70 mg/dL. Analyses were repeated with hypoglycemia defined as ≥ 60 mg/dL. Models were adjusted for admission glucose in addition to the covariates listed in Table 2.

### Table 4: Death at 30 Days by Group of Admission Glucose in Subjects With and Without Diabetes Mellitus

<table>
<thead>
<tr>
<th>Glucose Status</th>
<th>No. of Patients</th>
<th>Death at 30 d, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>424</td>
<td>32 (7.6)</td>
<td>1.20 (0.84–1.70)</td>
<td>1.04 (0.72–1.50)</td>
<td>0.85</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>14,916</td>
<td>950 (6.4)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9,554</td>
<td>1108 (11.6)</td>
<td>1.88 (1.72–2.04)</td>
<td>1.43 (1.30–1.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>35</td>
<td>8 (22.9)</td>
<td>3.12 (1.48–6.54)</td>
<td>2.13 (1.01–4.49)</td>
<td>0.0485</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>688</td>
<td>54 (7.9)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4,680</td>
<td>641 (13.7)</td>
<td>1.80 (1.36–2.38)</td>
<td>1.58 (1.19–2.10)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Hypoglycemia, normoglycemia, and hyperglycemia were defined as glucose ≤ 70, > 70 but ≤ 140, and > 140 mg/dL, respectively. Models were adjusted for the covariates listed in Table 2.
hyperglycemia nor hypoglycemia in the postadmission period predicted adverse outcomes. In addition, we found no association between postadmission hypoglycemia in patients treated or untreated with insulin (GIK) therapy, even though hypoglycemia was twice as common in patients who received insulin (GIK) therapy.

The present results are in contrast to prior studies that reported an association between hypoglycemia and adverse outcomes in AMI patients.\(^4\),\(^7\),\(^8\) One study of 4224 AMI patients reported a U-shaped relationship between glucose levels and the composite outcome of death or reinfarction at 30 days, with the highest event rate occurring in subjects with glucose \(< 81 \text{ mg/dL}\).\(^7\) However, only admission glucose (and not postadmission glucose) was measured, and the adverse association between hypoglycemia and clinical outcomes was restricted to the sickest patients on presentation (Thrombolysis in Myocardial Infarction risk score \(> 4\)). A second study\(^8\) was conducted in 713 diabetic patients with unstable angina or non-Q-wave myocardial infarction that found a statistically significantly higher mortality at 2 years among subjects with hypoglycemia (HR 1.93, 95% CI 1.18 to 3.17) than in those with normoglycemia; however, a causal link between in-hospital hypoglycemia and clinical outcomes ascertained 2 years later is difficult to establish, a much lower threshold was used to define hypoglycemia (\(< 55 \text{ mg/dL}\)), and non-diabetic subjects were not included. A third study\(^4\) determined that the best glucose metric for predicting in-hospital adverse outcomes was the mean in-hospital glucose, and that study also reported a U-shaped relationship between mean glucose and in-hospital mortality; however, the study did not describe outcomes associated with discrete episodes of hypoglycemia, which are more clinically relevant. The findings of the present study are more consistent with a recent analysis of the DIGAMI-2 trial (Diabetes mellitus Insulin-Glucose infusion in Acute Myocardial Infarction 2) in which in-hospital hypoglycemia did not predict adverse outcomes in 1253 diabetic patients with AMI after a median 2.1 years of follow-up.\(^10\) Another study of 7820 AMI patients reported no association between insulin-mediated hypoglycemia and in-hospital death, although spontaneous hypoglycemia (without preceding insulin administration) did predict death.\(^9\)

The present study adds valuable information to these prior studies. First, it is the largest study to date to evaluate the association between hypoglycemia and adverse outcomes in AMI patients, and it enables determination of how the prognostic significance of hypoglycemia or hyperglycemia might differ in important subgroups, such as patients with and without diabetes. Second, data were presented for admission and postadmission glucose separately and were analyzed as both glucose deciles (Figure 2), to show the relationship

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Table 5. Death at 30 Days by Group of Postadmission Glucose in Subjects With and Without Diabetes Mellitus

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Death at 30 d, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1153</td>
<td>49 (4.3)</td>
<td>0.91 (0.68–1.22)</td>
<td>0.89 (0.66–1.21)</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>10,511</td>
<td>488 (4.6)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>924</td>
<td>788 (8.5)</td>
<td>1.88 (1.68–2.10)</td>
<td>1.54 (1.36–1.74)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>91</td>
<td>10 (11.0)</td>
<td>1.75 (0.86–3.57)</td>
<td>1.58 (0.77–3.24)</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>490</td>
<td>31 (6.3)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4027</td>
<td>403 (10.0)</td>
<td>1.61 (1.12–2.32)</td>
<td>1.24 (0.85–1.82)</td>
</tr>
</tbody>
</table>

Hypoglycemia was defined as either 6- or 24-hour glucose \(\leq 70 \text{ mg/dL}\); normoglycemia as both postadmission glucose levels \(> 70 \text{ but } \leq 140 \text{ mg/dL}\); and hyperglycemia as at least 1 postadmission glucose \(>140 \text{ mg/dL}\) and neither value \(\leq 70 \text{ mg/dL}\). Models were adjusted for admission glucose in addition to the covariates listed in Table 2.

Table 6. Death at 30 Days by Group of Postadmission Glucose Levels Among Subjects Who Were and Were Not Allocated to Insulin (GIK) Therapy

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Death at 30 d, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No insulin (no GIK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>490</td>
<td>23 (4.7)</td>
<td>1.04 (0.68–1.59)</td>
<td>1.02 (0.67–1.56)</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>7649</td>
<td>343 (4.5)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6396</td>
<td>618 (9.7)</td>
<td>2.22 (1.94–2.53)</td>
<td>1.72 (1.48–2.00)</td>
</tr>
<tr>
<td>Insulin (GIK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypoglycemia</td>
<td>754</td>
<td>36 (4.8)</td>
<td>0.90 (0.63–1.29)</td>
<td>0.85 (0.59–1.24)</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>3352</td>
<td>176 (5.3)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6872</td>
<td>573 (8.3)</td>
<td>1.61 (1.36–1.91)</td>
<td>1.20 (1.00–1.44)</td>
</tr>
</tbody>
</table>

Hypoglycemia was defined as either 6- or 24-hour glucose \(\leq 70 \text{ mg/dL}\); normoglycemia as both postadmission glucose levels \(> 70 \text{ but } \leq 140 \text{ mg/dL}\); and hyperglycemia as at least 1 postadmission glucose \(>140 \text{ mg/dL}\) and neither value \(\leq 70 \text{ mg/dL}\). Models were adjusted for admission glucose in addition to the covariates listed in Table 2. GIK indicates glucose-insulin-potassium.
between glucose and outcomes across the spectrum of glucose levels, and as categories (hypoglycemia, normoglycemia, and hyperglycemia). We found that both the decile and categorical analyses were consistent in demonstrating an association between admission hypoglycemia and mortality that was attenuated in the postadmission period. This observation suggests that hypoglycemia may not be a direct mediator of adverse outcomes in AMI and may help reconcile the disparate results of prior studies that did not analyze admission and postadmission glucose separately. 

Third, the present study reported the association between hypoglycemia and outcomes in patients who were and were not treated with insulin. In the present study, insulin was administered as a component of fixed-dose GIK infusion that was not intended to achieve glucose lowering. Nevertheless, hypoglycemia was still twice as common in GIK-treated patients as in non–GIK-treated patients, which suggests that a substantial proportion of hypoglycemic episodes in GIK patients were in fact insulin induced. Importantly, we found no association between postadmission hypoglycemia and adverse outcomes in either insulin-treated or untreated patients in the present study, whereas the risk of hyperglycemia was observed in both groups. The lack of association between hypoglycemia and death in insulin-treated patients is consistent with the findings of another study in which insulin was administered to treat hyperglycemic AMI patients. 

The present study has limitations. Diabetes history was based on self-report, and the number of deaths in diabetic subjects with hypoglycemia was small (therefore, the CIs about the point estimates were wide). However, the diabetes subgroup was similar to the overall population in that admission hypoglycemia predicted death in diabetic patients, but this relationship became attenuated in the postadmission period. There were limited numbers of patients and events in the hypoglycemic group when defined as glucose ≤60 mg/dL, and therefore, the results for this subgroup should be considered exploratory. The present study did not document symptoms of hypoglycemia and therefore could not compare the prognostic significance of hypoglycemia with and without symptoms. Although we adjusted for important confounders of mortality in AMI, the present study did not capture other useful data, including the duration of diabetes; hemoglobin A1c levels (a marker of diabetes control before hospitalization); use of insulin or oral antidiabetic medications before or after hospital discharge; the presence of liver failure, kidney failure, or sepsis; or postdischarge glucose levels. These data in AMI patients also cannot be extrapolated to stable, chronically ill patients who may develop hypoglycemia in the outpatient setting. Finally, the present observational study does not imply that treating high or low glucose levels to achieve normoglycemia is beneficial in AMI patients. Professional societies recommend glucose control and avoidance of hypoglycemia in AMI patients, but they are based largely on expert consensus and interpretation of observational data. Adequately powered trials have yet to be conducted to determine the optimal strategy for managing hyperglycemia and hypoglycemia in hospitalized AMI patients.

In conclusion, the present study demonstrates that hyperglycemia in both the admission and postadmission period predicts death after AMI. In contrast, the relationship between hypoglycemia and mortality is confined to hospital admission and dissipates within the first 24 hours of AMI hospitalization. These observations suggest that hypoglycemia may not be a direct mediator of adverse events after AMI.

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Disclosures

Dr Goyal has received honoraria from Vascular Biology Working Group. Dr Gerstein received research grants from sanofi-aventis and honoraria from sanofi-aventis, Lilly, and Novo Nordisk and is a member of the advisory boards of sanofi-aventis and Lilly. The remaining authors report no conflicts.

References


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**CLINICAL PERSPECTIVE**

Hyperglycemia is a strong predictor of mortality in patients hospitalized with acute myocardial infarction. Professional society guidelines have accordingly advised glucose control in hyperglycemic patients. These same guidelines also recommend avoiding hypoglycemia, even though the association between hypoglycemia and adverse outcomes in acute myocardial infarction patients is controversial. We conducted a post hoc analysis of data from 2 large trials of glucose-insulin-potassium infusion in acute myocardial infarction and compared the prognostic significance of hypoglycemia and hyperglycemia with normoglycemia in 30,536 patients. Both hypoglycemia (glucose \( \leq 60 \text{ mg/dL} \)) and hyperglycemia (glucose \( \geq 140 \text{ mg/dL} \)) at admission predicted higher 30-day mortality. However, this U-shaped relationship became attenuated in the 24-hour postadmission period, during which hyperglycemia still predicted death but hypoglycemia no longer was prognostic. Results were similar in patients with a history of diabetes. Furthermore, even though hypoglycemia was more common in patients receiving insulin (glucose-insulin-potassium) therapy than in patients who did not, hypoglycemia did not predict death in either insulin-treated or untreated patients. This study suggests that hypoglycemia may not be a direct mediator of adverse outcomes in acute myocardial infarction patients and provides some reassurance to clinicians who are concerned about overlooking or unintentionally inducing hypoglycemia in these patients.
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Abhinav Goyal, Shamir R. Mehta, Rafael Díaz, Hertzle C. Gerstein, Rizwan Afzal, Denis Xavier, Lisheng Liu, Prem Pais and Salim Yusuf

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