Glucose Normalization and Outcomes in Patients With Acute Myocardial Infarction

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Background: Elevated blood glucose levels on admission are associated with increased mortality in patients with acute myocardial infarction. Whether glucose normalization after admission is associated with improved survival remains controversial. In addition, whether outcomes differ in patients who have spontaneous resolution of hyperglycemia vs those who achieve normoglycemia after treatment with insulin is also unknown.

Methods: We studied 7820 hyperglycemic (admission glucose level, ≥140 mg/dL [to convert glucose to millimoles per liter, multiply by 0.0555]) patients with acute myocardial infarction hospitalized between January 1, 2000, and December 31, 2005, in 40 US hospitals. Patients were stratified according to their mean glucose levels after admission and were divided into those who did and did not receive insulin therapy. Multivariable logistic regression models were developed to examine whether lower glucose levels after admission are independently associated with better survival. Propensity-matching methods were then used to compare in-hospital mortality in patients who did and did not receive insulin therapy.

Results: After multivariable adjustment, lower mean post-admission glucose levels were associated with better survival (for mean postadmission glucose levels of 110 to <140, 140 to <170, 170 to <200, and ≥200 mg/dL, the odds ratios [95% confidence intervals] were 2.1 [1.3-3.5], 5.3 [3.0-8.6], 6.9 [4.1-11.4], and 13.0 [8.0-21.3], respectively, vs <110 mg/dL). Similar results were seen in patients who did and did not receive insulin therapy (P=.74 for insulin therapy × postadmission glucose level interaction). In propensity-matched analysis, mortality rates were similar between insulin-treated and non-insulin-treated patients across the spectrum of mean post-admission glucose levels (range, P=.15 to P=.91).

Conclusions: Glucose normalization after admission is associated with better survival in hyperglycemic patients hospitalized with acute myocardial infarction whether or not they receive insulin therapy. A strategy of intentional glucose lowering with insulin therapy needs to be further tested in future randomized controlled trials.

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Although a strong association between elevated blood glucose levels and increased mortality in patients hospitalized with acute myocardial infarction (AMI) has been documented, the benefit of lowering glucose levels with pharmacologic therapy remains controversial.1-26 Current American College of Cardiology and American Heart Association practice guidelines recommend strict glucose control in patients with AMI27,28 but supportive evidence is limited. Prior clinical trials of glucose control in patients with AMI have produced inconsistent results29-31 and had numerous limitations, including insufficient sample size and inability to demonstrate substantial contrast in glucose control between the intervention and control groups.

As a result, critical questions in this field remain unanswered, as recently highlighted by the American Heart Association’s scientific statement on hyperglycemia and acute coronary syndrome.32 First, whether normalization of glucose levels after admission is associated with improved survival in hyperglycemic patients with AMI is unknown, and the specific range of glucose levels associated with the lowest mortality has not been established, to our knowledge. Second, whether insulin therapy is associated with any clinical benefit in AMI beyond its associated glucose-lowering effect remains a subject of debate, and whether the prognostic implications of glucose normalization differ in hyperglycemic patients who do and do not receive insulin therapy remains unclear. Because of these knowledge gaps, there is uncertainty about how to best care for patients with AMI who have elevated glucose levels. Addressing these questions could provide initial guidance.
for patient care and could inform future prospective clinical trials regarding the intensity of glucose control that should be targeted.

Accordingly, we analyzed data from Cerner Corporation’s (Kansas City, Missouri) Health Facts database, a national contemporary database of patients hospitalized with AMI in 40 hospitals across the United States. This database provides a unique opportunity to define the relationship between glucose lowering and patient outcomes associated with AMI, as it contains detailed information regarding glucose measurements and insulin therapy in a large group of patients. We specifically sought to determine whether glucose normalization after AMI admission is associated with better survival in patients with initial hyperglycemia, to define postadmission glucose levels associated with the lowest mortality, and to establish whether the prognosis associated with lower postadmission glucose levels differs in patients who did and did not receive insulin therapy.

DETAILS ABOUT THE HEALTH FACTS DATABASE HAVE BEEN PREVIOUSLY DESCRIBED.26 Health Facts captures deidentified patient data from the contributor institutions’ electronic health records; rigorous quality assurance efforts and audits occur on a regular basis to ensure data accuracy. All 40 participating medical centers in the Health Facts consortium contributed deidentified information on consecutive patients treated between January 1, 2000, and December 31, 2005. Data included the following demographics, in-hospital mortality, comprehensive pharmacy data, comprehensive laboratory data (including all venous and fingerstick blood glucose measurements during hospitalization), in-hospital procedures (including cardiac catheterization, coronary artery bypass surgery, and percutaneous coronary intervention), medical history and comorbidities (determined from International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnostic codes), and hospital characteristics (such as number of beds, geographic region, teaching vs nonteaching status, and presence of cardiothoracic surgery facilities and cardiac catheterization and angioplasty facilities).

STUDY COHORT

We identified 23613 patients hospitalized with the primary diagnosis of AMI between January 1, 2000, and December 31, 2005 (using ICD-9-CM codes 410.xx and excluding 410.x2, which represents readmission after AMI), who had at least 1 glucose measurement during the first 24 hours following admission and at least 1 documented abnormal troponin I or T value or creatine kinase MB fraction. Subsequently, 6742 patients who were transferred from or to other acute care facilities were excluded from the study, as complete laboratory and medication administration details for their entire episode of AMI care were unavailable. We also excluded 8218 patients whose admission glucose level was lower than 140 mg/dL (to convert glucose level to millimoles per liter, multiply by 0.0555), as these patients would typically not be considered candidates for pharmacologic glucose lowering in this setting, as well as 833 patients who had no additional glucose measurements following admission (in patients who did not receive insulin therapy) or after initiation of insulin therapy (in insulin-treated patients) because their subsequent glucose levels could not be ascertained. Our final cohort comprised 7820 hyperglycemic patients with biomarker-confirmed AMI.

INPATIENT GLUCOSE ASSESSMENT

The Health Facts database provided access to all patients’ glucose levels (capillary and plasma assessments), including time of measurement. Whole blood glucose specimens were converted by glucose meters into plasma glucose values (in units of milligrams per deciliter) for all analyses (plasma glucose level × whole blood glucose level × 1.15). For clarity, all plasma and capillary glucose measurements are subsequently referred to as blood glucose.

In all patients, 2 glucose metrics were assessed. The first metric was admission glucose level. In patients who received insulin therapy, the second metric was the mean posttreatment glucose level, which is the mean of all glucose levels obtained after the first insulin dose was administered. For patients who did not receive insulin therapy during their hospitalization, the second metric was the mean postadmission glucose level, which is the mean of all glucose levels obtained after the initial measurement. For clarity, the mean glucose metric for patients who did and did not receive insulin therapy is subsequently referred to as postadmission glucose level. It was previously demonstrated that the mean glucose level is the optimal metric of in-hospital glucose control.26

To simplify the interpretation of results, patients were stratified as follows according to their mean postadmission glucose levels: lower than 110, 110 to lower than 140, 140 to lower than 170, 170 to lower than 200, and 200 mg/dL or higher. In addition, postadmission glucose levels were analyzed in increments of 10 mg/dL.

INSULIN THERAPY AND DIABETES DEFINITION

Analyses were performed in the entire patient cohort and were then repeated in subgroups of patients who did and did not receive insulin therapy. In addition, given previous findings that the nature of the association between elevated glucose levels and outcomes differs in patients with and without diabetes mellitus (DM),1,20,26,33 analyses were repeated in subgroups of patients with and without known DM.

Administration of any insulin during hospitalization (whether subcutaneous versus intravenous or short acting versus long acting) was considered insulin therapy. The time of insulin administration was recorded for all treated patients. This information was ascertained directly from the Health Facts database. Patients were classified as having recognized DM if they had a corresponding ICD-9-CM code or were treated with an oral antihyperglycemic agent or any extended-release insulin during hospitalization.

OUTCOMES

The outcome for this study was all-cause in-hospital mortality. This information was obtained directly from the Health Facts database.

STATISTICAL ANALYSIS

Baseline Characteristics

Baseline demographic and clinical characteristics were compared across the 5 postadmission glucose levels using the Pearson χ² test for categorical variables. Analysis of variance was used for continuous variables.
Association Between Postadmission Glucose Levels and Mortality

To assess whether lower postadmission glucose levels are associated with better survival, mortality rates were compared across the 5 postadmission glucose levels using the χ² test. Multivariable logistic regression models were subsequently developed to evaluate whether the association between mean postadmission glucose levels and mortality persisted after adjustment for other patient characteristics and for potential confounders. In these models, the mean postadmission glucose levels were modeled initially as a categorical variable (using the 5 levels as already described). In addition, postadmission glucose levels were modeled in increments of 10 mg/dL to ascertain specific glucose levels associated with the lowest mortality. Patient characteristics considered prognostically important and all covariates identified in bivariate analyses as predictors of in-hospital mortality were entered into the models. Covariates included the following: peak troponin or creatine kinase MB value, demographic factors (age, sex, and race/ethnicity), laboratory values on admission (hematocrit, creatinine level, and white blood cell count), procedures during hospitalization (cardiac catheterization, percutaneous intervention, and coronary artery bypass grafting), comorbidities (DM, dementia, heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease), and medications during hospitalization (statins, nitrates, aspirin, diuretics, β-blockers, bronchodilators, clopidogrel bisulfate, ticlopidine hydrochloride, calcium channel blockers, and oral antihyperglycemic agents).

Most important, models were also adjusted for the admission glucose level given its known association with mortality in patients with AMI. Furthermore, analyses were adjusted for clustering by site, for hospital length of stay, and for frequency of glucose testing, as the intensity of testing could be related to severity of hyperglycemia and to in-hospital mortality. Analyses were repeated within subgroups of patients who presented only if they received insulin therapy within the first 24 hours after admission (likely as a reaction to their initial insulin doses; 59.0% received only short-acting insulin, 2.7% received only long-acting insulin, and 38.3% received both. Seventeen percent of insulin-treated patients received intravenous insulin. The median number of glucose measurements following the admission assessment was 6 (interquartile range, 3-15) in insulin-treated patients and 3 (interquartile range,
2-7) in patients who did not receive insulin therapy; 44.2% of all glucose measurements occurred during the first 72 hours of hospitalization and 55.8% after the first 72 hours. The median length of stay was 127 hours (interquartile range, 79-206 hours) in the entire cohort, 115 hours (interquartile range, 73-183 hours) in patients who did not receive insulin therapy, and 150 hours (interquartile range, 91-253 hours) in insulin-treated patients. The median number of glucose measurements did not vary substantially by mean postadmission glucose levels (for postadmission glucose levels of <110, 110 to <140, 140 to <170, 170 to <200, and ≥200 mg/dL, the median [interquartile range] numbers of measurements were 5 [3-8], 6 [4-12], 7 [4-13], 7 [4-14], and 6 [3-13], respectively). The median time to first postadmission glucose assessment was similar in insulin-treated and non-insulin-treated patients.

UNADJUSTED ASSOCIATION BETWEEN POSTADMISSION GLUCOSE LEVELS AND MORTALITY

In the unadjusted analyses, lower postadmission glucose levels were associated with better survival (for postadmission glucose levels of <110, 110 to <140, 140 to <170, 170 to <200, and ≥200 mg/dL, mortality was 3.1%, 5.7%, 10.8%, 11.6%, and 19.6%, respectively; \( P < .001 \) for overall comparison). Similar results were observed in patients who did and did not receive insulin therapy (Table 2).

ADJUSTED ASSOCIATION BETWEEN POSTADMISSION GLUCOSE LEVELS AND MORTALITY

After multivariable adjustment, the relationship between higher postadmission glucose levels and in-
increased in-hospital mortality persisted (Table 3). Mortality was lowest in patients with postadmission glucose levels lower than 110 mg/dL and increased with higher postadmission glucose levels (for postadmission glucose levels of 110 to <140, 140 to <170, 170 to <200, and ≥200 mg/dL, the odds ratios [95% confidence intervals] were 2.1 [1.3-3.5], 5.3 [3.0-8.6], 6.9 [4.1-11.4], and 13.0 [8.0-21.3], respectively, vs <110 mg/dL). Overall, the results were similar in both groups (data not shown).

When postadmission glucose levels were analyzed in increments of 10 mg/dL, there was a statistically significant, consistent, and gradual increase in the odds of inhospital mortality with each incremental rise in mean postadmission glucose levels above the threshold of 130 mg/dL (eg, for patients with a glucose level of 130 to <140 mg/dL, the odds ratio [95% confidence interval] was 3.0 [1.6-5.9] vs 100 to <110 mg/dL (Figure 1). There was also a slight increase in the odds of mortality with postadmission glucose levels below 80 mg/dL; however, it was not statistically significant.

When models were repeated within groups of patients who did and did not receive insulin therapy, no significant differences were observed in baseline characteristics between the insulin-treated and non–insulin-treated patients, indicating an excellent match between the groups (Table 4). Mortality for propensity-matched insulin-treated and non–insulin-treated patients across 5 postadmission glucose levels is shown and directly compared in Figure 2. There were no statistically significant differences between the treated and nontreated patients at any of the 5 postadmission glucose levels, and the overall effect of insulin therapy on mortality was not statistically significant (P=.07). The relationship between lower postadmission glucose levels and reduced mortality continued to be observed in insulin-treated and non–insulin-treated patients. Results obtained from the propensity-matched model that selected insulin-treated patients only if they received insulin therapy within the first 24 hours after admission were similar (data not shown).

DIRECT COMPARISON OF INSULIN-TREATED AND NON–INSULIN-TREATED PATIENTS

There were 1774 propensity-matched pairs of patients who did and did not receive insulin therapy. No significant differences were observed in baseline characteristics between the insulin-treated and non–insulin-treated patients, indicating an excellent match between the groups (Table 4). Mortality for propensity-matched insulin-treated and non–insulin-treated patients across 5 postadmission glucose levels is shown and directly compared in Figure 2. There were no statistically significant differences between the treated and nontreated patients at any of the 5 postadmission glucose levels, and the overall effect of insulin therapy on mortality was not statistically significant (P=.07). The relationship between lower postadmission glucose levels and reduced mortality continued to be observed in insulin-treated and non–insulin-treated patients. Results obtained from the propensity-matched model that selected insulin-treated patients only if they received insulin therapy within the first 24 hours after admission were similar (data not shown).

COMMENT

In this large contemporary cohort of hyperglycemic patients hospitalized with AMI, we demonstrate that a decrease in glucose level after admission (whether spontaneous or following insulin therapy) is associated with a significant reduction in in-hospital mortality, even after adjusting for numerous potentially confounding patient and treatment characteristics. Although we had somewhat limited data regarding the intensity of insulin administration, our findings suggest that insulin therapy per se is not independently associated with a survival advantage. Rather,
it is glucose normalization (mediated by a glucose-lowering effect of insulin therapy in some patients) that seems to be associated with better survival. Specifically, patients with postadmission glucose levels of 80 to 130 mg/dL experienced the lowest mortality.

Prior randomized clinical trials and observational studies have been unable to test the hypothesis that insulin-mediated normoglycemia would be associated with improved outcomes in hyperglycemic patients with AMI. The original Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI)29 clinical trial showed that modest glucose lowering using glucose-insulin infusion improved survival in patients with DM and AMI compared with usual care. However, treatment targets used in the DIGAMI trial (glucose levels of 126-196 mg/dL) were much higher than what would now be considered the normoglycemic range. Subsequent DIGAMI 230 and Hyperglycemia: Intensive Insulin Infusion in Infarction31 clinical trials were unable to achieve substantial contrasts in glucose levels between the intervention and control arms, undermining their ability to detect a difference in outcomes between treatment and control patients. A post hoc analysis of Complement and Reduction of Infarct Size After Angioplasty or Lytics32 clinical trial data found that a further increase in glucose level during the first 24 hours of hospitalization was associated with higher 30-day and 180-day mortality in hyperglycemic patients with AMI, while a decrease in glucose level was associated with improved survival. However, because of data limitations, this study did not differentiate between spontaneous and insulin-mediated decreases in glucose levels, nor did it identify a specific range of glucose levels associated with the most optimal patient outcomes.

Our findings substantially add to the current understanding of the relationship between glucose normalization and outcomes in hyperglycemic patients with AMI and address some of the important knowledge gaps highlighted in the American Heart Association’s scientific statement on hyperglycemia and acute coronary syndrome.32 Using unique features of our database, including detailed information about glucose measurements and insulin therapy, and the ability to perform detailed subgroup analyses because of the large sample size, we determined that postadmission glucose normalization is associated with improved survival. In addition, our findings suggest that targeting posttreatment glucose levels of about 80 to 130 mg/dL may represent a reasonable initial strategy in this patient group. Because a causal relationship between glucose normalization and improved survival cannot be established based on the results of our study, testing these potential treatment targets in large properly designed randomized clinical trials is the next logical and necessary step before their implementation in routine clinical practice.

Whether any potential benefits of glucose control in a setting of AMI may primarily be due to glucose normalization, insulin administration, or both has been a subject of debate. Prior studies35-43 have shown that insulin therapy may improve myocardial blood flow, may inhibit generation of reactive oxygen species, and may have anti-inflammatory, profibrinolytic, and antiapoptotic properties. However, if some of these pleiotropic effects of insulin therapy were important determinants of outcome, then we should have observed better outcomes among insulin-treated patients independent of glucose control. Instead, our data suggest that ineffective insulin therapy (ie, treatment that does not produce normalization of glucose levels) is not associated with better out-
comes. In fact, in our study there was no significant difference in mortality between patients who remained hyperglycemic following insulin administration and those who remained hyperglycemic without receiving treatment. It was glucose normalization that was associated with better survival. Similar observations were made in prior randomized trials of glucose-insulin-potassium therapy, in which lower postrandomization glucose level, but not treatment with glucose-insulin-potassium, was associated with lower mortality.44 Therefore, we believe that any possible benefits of insulin therapy are likely mediated through the control of blood glucose level and that it is glucose level, rather than insulin therapy per se, that seems to be a more important predictor of patient outcomes. It is inherently difficult to predict which hyperglycemic patients with AMI will have spontaneous normalization of glucose levels and which will require insulin therapy. Therefore, a potential initial approach, which needs to be tested in future clinical trials, may be initiation of insulin therapy with the goal of glucose normalization in hyperglycemic patients with AMI, regardless of DM history.

Recent randomized clinical trials showed that long-term intensive glucose control in outpatients with type 2 DM did not significantly reduce the rate of macrovascular disease events.45,46 Although the questions addressed by these clinical trials and by our study are somewhat related, the patient populations and clinical strategies under study are distinctly different. The clinical trials evaluated a strategy of intensive long-term glucose lowering in outpatients with type 2 DM (some with preexisting coronary artery disease). In contrast, our study examines the relationship between acute glucose normalization and in-hospital mortality in patients hospitalized with AMI. Therefore, the results of the Action to Control Cardiovascular Risk in Diabetes45 and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation46 trials cannot be extrapolated to the acute and transient management of hyperglycemia in patients hospitalized with AMI. Instead, an appropriately designed randomized clinical trial of target-driven glucose lowering will be necessary to establish whether this strategy is effective in improving outcomes in this patient population.

### Table 4. Baseline Characteristics of Propensity-Matched Insulin-Treated and Non–Insulin-Treated Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Insulin Therapy (n=1774)</th>
<th>No Insulin Therapy (n=1774)</th>
<th>P Value</th>
<th>Standardized Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.2 (12.7)</td>
<td>71.9 (12.3)</td>
<td>.09</td>
<td>-5.63</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>47.7</td>
<td>46.8</td>
<td>.61</td>
<td>1.69</td>
</tr>
<tr>
<td><strong>Clinical Features, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>49.0</td>
<td>50.7</td>
<td>.31</td>
<td>-3.38</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54.4</td>
<td>54.3</td>
<td>.97</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.2</td>
<td>4.0</td>
<td>.74</td>
<td>1.14</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5.5</td>
<td>6.3</td>
<td>.32</td>
<td>-3.34</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.8</td>
<td>2.5</td>
<td>.13</td>
<td>-5.03</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>12.2</td>
<td>12.2</td>
<td>&gt;.99</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67.6</td>
<td>66.1</td>
<td>.34</td>
<td>3.19</td>
</tr>
<tr>
<td><strong>In-Hospital Procedures, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>44.4</td>
<td>43.4</td>
<td>.57</td>
<td>1.93</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>23.6</td>
<td>23.1</td>
<td>.72</td>
<td>1.20</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>9.2</td>
<td>8.3</td>
<td>.31</td>
<td>3.39</td>
</tr>
<tr>
<td><strong>Admission Laboratory Values, Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.6 (1.2)</td>
<td>1.6 (1.3)</td>
<td>.39</td>
<td>-2.88</td>
</tr>
<tr>
<td>White blood cell count, /µL</td>
<td>11 900 (6100)</td>
<td>11 800 (7700)</td>
<td>.96</td>
<td>0.18</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>36.9 (9.7)</td>
<td>36.9 (9.9)</td>
<td>&gt;.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak troponin, ng/mL</td>
<td>56.1 (133.0)</td>
<td>56.1 (133.0)</td>
<td>.82</td>
<td>0.00</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>241.0 (88.0)</td>
<td>238.0 (93.5)</td>
<td>.34</td>
<td>3.24</td>
</tr>
<tr>
<td><strong>Length of Stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), h</td>
<td>174.7 (147.6)</td>
<td>175.0 (170.1)</td>
<td>.95</td>
<td>-0.19</td>
</tr>
<tr>
<td><strong>In-Hospital Medications, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>83.4</td>
<td>82.5</td>
<td>.50</td>
<td>2.25</td>
</tr>
<tr>
<td>Other platelet inhibitors</td>
<td>48.3</td>
<td>47.4</td>
<td>.61</td>
<td>1.69</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>85.1</td>
<td>85.2</td>
<td>.89</td>
<td>-0.48</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>27.6</td>
<td>28.0</td>
<td>.82</td>
<td>-0.76</td>
</tr>
<tr>
<td>Diuretics</td>
<td>65.6</td>
<td>65.1</td>
<td>.75</td>
<td>1.07</td>
</tr>
<tr>
<td>Nitrates</td>
<td>84.1</td>
<td>83.4</td>
<td>.55</td>
<td>1.99</td>
</tr>
<tr>
<td>β-Adrenergic bronchodilators</td>
<td>24.3</td>
<td>24.0</td>
<td>.85</td>
<td>0.66</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme/angiotensin receptor blocker</td>
<td>69.3</td>
<td>67.8</td>
<td>.35</td>
<td>3.16</td>
</tr>
<tr>
<td>Statins</td>
<td>58.3</td>
<td>57.4</td>
<td>.61</td>
<td>1.71</td>
</tr>
<tr>
<td>Oral antihyperglycemic agents</td>
<td>20.5</td>
<td>20.0</td>
<td>.71</td>
<td>1.24</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert glucose level to millimoles per liter, multiply by 0.0555; creatinine level to micromoles per liter, multiply by 88.4; white blood cell count to ×10^9/L, multiply by 0.001; hematocrit to proportion of 1.0, multiply by 0.01; troponin level to micrograms per liter, multiply by 1.0.
The results of our study should be interpreted in the context of several possible limitations. First, given the retrospective nature of the analyses, a possibility of residual confounding cannot be entirely excluded. Although we rigorously attempted to account for baseline differences between patients in different postadmission glucose groups and between those who did and did not receive insulin therapy (including the use of propensity matching), residual unmeasured differences may persist. Specifically, we were unable to control for several clinical variables such as left ventricular ejection fraction after AMI and the presence of ST-segment elevations. However, adjustment for left ventricular ejection fraction did not have much influence on the prognostic effect of glucose levels in prior analyses,1 and we were able to control for other more important measures of infarct severity such as peak troponin or creatine kinase MB value and multiple other clinical factors. Second, causal relationship between glucose normalization and improved outcomes cannot be established from this study. It is possible that, despite extensive statistical adjustment, glucose lowering is a marker of improvement in patients’ overall clinical course rather than a direct mediator of better survival. Third, we had somewhat limited data regarding the intensity of insulin administration. However, given a paucity of firmly established protocols guiding insulin administration in hyperglycemic patients with AMI, our study reflects routine clinical care. Fourth, because of limited follow-up, we could not assess the effect of glucose normalization on long-term outcomes.

In conclusion, glucose normalization is associated with lower mortality among initially hyperglycemic patients hospitalized with AMI whether or not they receive insulin therapy. The strategy of target-driven glucose lowering in this patient group should be further tested in randomized clinical trials.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kosiborod, Inzucchi, and Goyal. Acquisition of data: Kosiborod and Fiske. Analysis and interpretation of data: Kosiborod, Inzucchi, Krumholz, Masoudi, Goyal, Xiao, Jones, and Spertus. Drafting of the manuscript: Kosiborod and Xiao. Critical revision of the manuscript for important intellectual content: Kosiborod, Inzucchi, Krumholz, Masoudi, Goyal, Xiao, Jones, Fiske, and Spertus. Statistical analysis: Kosiborod, Xiao, and Jones. Obtained funding: Kosiborod and Spertus. Administrative, technical, and material support: Kosiborod and Spertus. Study supervision: Kosiborod, Inzucchi, and Spertus.

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References


