Glucose Variability and Mortality in Patients Hospitalized With Acute Myocardial Infarction

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Background—Mean blood glucose (BG) during acute myocardial infarction (AMI) is an important predictor of inpatient mortality but does not capture glucose variability (GV), which has been shown to be independently associated with mortality in critically ill patients. Whether GV is associated with in-hospital mortality during AMI, after accounting for mean BG, is unknown.

Methods and Results—We analyzed 18 563 consecutive patients with AMI with ≥3 BGs in the first 48 hours admitted to 61 US hospitals from 2000 to 2008. Five different GV metrics were compared for their ability to predict in-hospital mortality (range, standard deviation, mean amplitude of glycemic excursions, mean absolute glucose change, and average daily risk range) using hierarchical logistic regression models that sequentially adjusted for mean BG, hypoglycemia (<70 mg/dL), and multiple patient characteristics. In unadjusted analyses, range and average daily risk range had the highest C-indices (0.620 for range, 0.635 for average daily risk range; both P<0.0001). Greater GV was associated with higher mortality for all metrics (eg, mortality was 3.8%, 5.5%, 7.1%, and 11.3% for increasing quartiles of range; P<0.0001); however, the association between GV and mortality for each metric was no longer significant after multivariable adjustment. In contrast, mean BG remained an important predictor of survival (P<0.001, all models).

Conclusions—Although greater GV is associated with increased risk of in-hospital mortality in patients with AMI in unadjusted analyses, GV is no longer independently predictive after controlling for multiple patient factors, including mean BG. These findings suggest that GV does not provide additional prognostic value above and beyond already recognized risk factors for mortality during AMI. (Circ Cardiovasc Qual Outcomes. 2012;5:00-00.)

Key Words: glucose variability ■ acute myocardial infarction ■ prognosis ■ diabetes mellitus ■ glucose

Previous studies have demonstrated that admission blood glucose (BG) during acute myocardial infarction (AMI) is an important predictor of mortality.9–14 Persistent hyperglycemia during hospitalization, expressed as mean BG, predicts mortality better than admission BG9; however, mean BG does not capture the variability in glucose values during inpatient stays. Physiological studies have suggested several mechanisms through which glucose variability (GV) may adversely impact prognosis in the setting of AMI, including oxidative stress,10 cytokine release,11 and endothelial dysfunction.12 In addition, GV has been associated with adverse events in other critically ill patient populations13–22; however, neither the appropriate metric of GV nor its prognostic significance has been defined in the setting of AMI.

To address these knowledge gaps, we analyzed the data from Cerner Corporation’s Health Facts, a contemporary national database of patients hospitalized with AMI in 61 US centers between 2000 and 2008. Health Facts provided a unique opportunity to answer these questions, as it contains detailed information on routinely obtained BG measurements in a large, unselected population of patients with AMI. Specifically, we sought to identify GV metrics that are most predictive of in-hospital mortality and to examine whether GV provides additional prognostic information above and beyond mean BG.

Methods

Data Source

Cerner’s Health Facts database had been previously used to examine the association of various blood glucose metrics with inpatient mortality in critically ill patients.13–22; however, neither the appropriate metric of GV nor its prognostic significance has been defined in the setting of AMI.

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mortality. This database captures de-identified data from the Cerner electronic medical record of patients admitted to participating hospitals between January 1, 2000, and December 31, 2008. Compiled data include hospital characteristics, patients’ demographic characteristics (from medical records and registration data), medical history, and comorbidities (using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] codes), laboratory studies (including venous and capillary [fingerstick] blood glucose values), in-hospital medications, procedures, and complications. The median number of patients from each hospital was 219 (25th to 75th percentile range [Q1, 48; Q3, 103]) and the median duration of hospitals’ participation with the database was 2.9 years (Q1, 1.2; Q3, 5.3). Health Facts hospitals were frequently urban (88.5%), teaching hospitals (35.9%), and represented all geographic regions of the United States (Northeast, 38.5%; Midwest, 25.6%; South, 26.9%; and West, 9%) and a broad range of sizes (bed size 1 to 99, 26.9%; 100 to 199, 20.5%; 200 to 299, 23.1%; 300 to 499, 17.9%; and ≥500 beds, 11.5%). A total of 61 participating medical centers contributed data to this study.

WHAT IS KNOWN

• Mean blood glucose is an important predictor of in-hospital mortality in the setting of acute myocardial infarction but does not capture glucose fluctuations.
• Whether glucose variability adds incremental prognostic value above and beyond mean glucose in patients with myocardial infarction is not known.

WHAT THE STUDY ADDS

• Several metrics of glucose variability based on routinely collected blood glucose data are associated with mortality during acute myocardial infarction; however, glucose variability is no longer independently predictive after controlling for multiple patient factors, including mean blood glucose.
• The role of glucose variability should be further investigated in clinical studies where blood glucose values are frequently and systematically collected.

Study Cohort

We identified all patients hospitalized with a primary discharge diagnosis of AMI between January 2000 and December 2008 (using ICD-9 codes 410.xx and excluding 410.x2, which represents readmission after AMI), who had at least 1 elevated troponin I or T or creatine kinase muscle-brain fraction (n = 39,759) (Figure 1). We defined an exposure period (the first 48 hours) and the follow-up period (>48 hours and ≤31 days) to establish distinct exposure and follow-up times. We chose the first 48 hours specifically because we hypothesized that GV may be particularly important during the early acute phase of AMI. We therefore excluded patients who were discharged or died within the first 48 hours (n = 5,921). Other exclusion criteria included (1) transfers from other acute care facilities or hospice (n = 72), because complete laboratory details for the patient’s hospitalization were not available; (2) length of stay >31 days (n = 394), as these patients are not representative of the typical AMI population; and (3) those with extreme hyperglycemia (defined as plasma glucose >1000 mg/dL) (n = 40), as this extent of BG excursion likely represents a separate process from GV typically encountered in the AMI setting. Finally, we excluded patients with <3 glucose values within the first 48 hours because we could not reliably estimate GV with fewer measures (n = 14,769). Our final cohort included 18,563 patients with biomarker-confirmed AMI and at least 3 BG measurements within the first 48 hours of hospitalization.

Inpatient Glucose Assessment

Both capillary and plasma BG assessments during the first 48 hours of hospital admission were included. We excluded values <10 or >600 mg/dL obtained on capillary blood samples, as these are outside of the valid range for most hospital meters.

Candidate Glucose Variability Metrics

To identify the most prognostically important measures of GV during AMI, we compared the following candidate metrics for their ability to best discriminate survivors from nonsurvivors: standard deviation (SD), mean amplitude of glucose excursions, mean absolute glucose change (MAG), and average daily risk range (ADRR). We also added range (difference between the maximum and minimum BG values during the 48 hours) as one of the candidate metrics, although, admittedly, the value of range may depend on the number of glucose assessments. We felt it important to include range based on its ease of calculation and clinical implementation.

Diabetes and Insulin Therapy Definitions

Congruent with prior work, patients were classified as having diabetes by ICD-9 code or treatment with oral antihyperglycemic agent or any extended-release insulin during hospitalization. Administration of any insulin during hospitalization (whether subcutaneous versus intravenous or short-acting versus long-acting) was considered insulin therapy. Hypoglycemia was defined based on at least 1 BG <70 mg/dL during the first 48 hours.

Type of AMI

We defined the type of AMI based on the following ICD-9 codes: 410.0x to 410.6x or 410.8x as ST-segment–elevation myocardial infarction (STEMI), 410.7x as non-STEMI (NSTEMI), and 410.9x as unknown AMI. Although ICD-9 coding descriptions changed in 2005, the correlation between NSTEMI by electrocardiogram (EKG) criteria, and ICD-9 codes did not change substantially before and after this period.

Outcomes

The outcome for this study was all-cause, in-hospital mortality, as obtained directly from the Cerner Health Facts database following the first 48 hours of hospitalization.

Statistical Analysis

Baseline Characteristics

To compare baseline characteristics between patients with various degrees of GV, we stratified patients by GV quartiles. Baseline demographic and clinical characteristics were compared across the 4 groups. Continuous variables were compared using linear trend tests,
and categorical variables were compared using Mantel-Haenszel trend tests.

**Comparison of Glucose Variability Metrics**

To assess the discriminatory ability of the 5 GV metrics, we constructed individual hierarchical logistic regression models, with each GV metric as an independent variable and in-hospital mortality as the outcome. The discriminating ability of each GV metric was estimated using the C-index. C-index is a measure of how well a model correctly rank-orders patients by risk. A model that accurately discriminates patients 75% of the time would have a C index of 0.75; with completely random predictions, such as a coin toss, the C index would be 0.5; and a model that discriminates perfectly between patients with and without events would have a C index of 1.0. Pairwise comparisons between the C-indices were performed using the DeLong test.

**Multivariable Models**

Hierarchical multivariable logistic regression models were constructed to assess whether the association between GV and in-hospital mortality was independent of other factors. We sequentially adjusted for mean BG, then mean BG and hypoglycemia (<70 mg/dL), and, finally, adding the patient characteristics to create a fully adjusted model. Patient factors typically available to physicians during the initial 48-hour exposure period that were either demonstrated or clinically considered to be important predictors of in-hospital mortality included demographics (age, sex, race), comorbidities (heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia), and laboratory values on admission (creatinine, white blood cell count, hematocrit, peak troponin value).

We also used the integrated discrimination improvement method to assess the incremental benefit of adding GV to a model containing mean BG. Integrated discrimination improvement measures the ability of the additional risk factor (in our case, GV) to increase the predicted probability among those who had an event and to decrease the predicted probability among those who were event-free. Thus, in our analysis, integrated discrimination improvement measures the ability of GV to increase the predicted probability of in-hospital death among those who died and to decrease the predicted probability among those who survived, when added to a model containing mean BG.

**Subgroup Analyses**

Interactions between GV metrics and diabetes status, insulin use, mean BG, and STEMI versus NSTEMI status were evaluated. Mean BG categories were defined based on prior work and were categorized as follows: <110 mg/dL (n=3372), 110 to <140 mg/dL (n=6420), 140 to <170 mg/dL (n=3631), 170 to <200 mg/dL (n=2084), and ≥200 mg/dL (n=3056). Stratified analyses were performed when statistically significant interactions were identified. These subgroup analyses were conducted using the 2 best GV metrics (based on highest C-index in unadjusted models) to avoid the finding of spurious associations due to multiple comparisons.

**Sensitivity Analysis**

Although our aim was to assess the relationship between GV with hospital survival based on routinely collected BG values during AMI, it is possible that 3 BG values during the first 48 hours of hospital stay may not adequately capture GV during AMI. GV is best examined via continuous glucose monitoring or hourly glucose measures; however, these are not generally performed in routine clinical practice. To address this issue, we conducted a sensitivity analysis to examine whether more frequent BG monitoring may impact the relationship between GV and outcomes. In this analysis, we included only patients with 6 or more BG values during the first 48 hours (n=4396). We calculated C indices for the GV metrics and proceeded with the stepwise multivariable logistic regression as described previously.

**Role of the Funding Source**

Cerner Corporation collected the Heath Facts data. All data were de-identified before they were provided to the investigators; accordingly, an exemption from institutional review board (IRB) review was provided by the Saint Luke’s Hospital Institutional Review Board. Cerner Corporation provided the data but had no role in study funding, design, analyses, manuscript drafting, or review of the manuscript.

**Results**

**Baseline Characteristics**

Baseline characteristics of 18,563 patients across increasing GV quartiles (shown, as an example, for range) are detailed in Table 1. Patients in the higher GV quartiles were older, more likely to be female, had more comorbidities (heart failure, lung disease), and underwent fewer percutaneous coronary intervention and angiography procedures than those in the lower quartiles. In addition, diabetes was present in the majority of patients in the highest quartile of range (72.3%) but only in the minority in the lowest quartile of range (10.1%). Patients in the highest GV quartile had higher admission creatinine, lower admission hematocrit, higher admission and mean glucose in the first 48 hours, and were treated more frequently with insulin and oral antihyperglycemic agents.

The median number of glucose measurements in the overall sample was 3, with 25% and 75% percentiles, 3 and 5, respectively.

**Comparison of Glucose Variability Metrics**

A description of the calculation for each GV metric is provided in the legend of Table 2. In unadjusted analyses, greater GV was associated with increased risk of in-hospital mortality for all metrics (Table 2). C-indices for unadjusted models for each of the GV metrics were 0.606 for SD, 0.578 for mean amplitude of glucose excursions, 0.619 for MAG, 0.620 for range, and 0.635 for ADRR (all P<0.0001; probability value comparing across indices, P<0.0001). The C-index for mean BG during the first 48 hours was 0.644 (P<0.0001).

**Multivariable Models**

After sequentially adjusting for mean BG, hypoglycemia, and patient characteristics, none of the GV metrics were statistically significant in the models (see Table 3). In contrast, mean BG remained a significant independent predictor of in-hospital mortality in fully adjusted models.

The integrated discrimination improvement was not statistically significant when any of the GV metrics were added to the mean BG model. Thus, the differences in predicted average risk for in-hospital death between the model containing mean BG and models containing both mean BG and each GV metric were not significant. In addition, there was a significant correlation between the GV metrics and mean BG, with the Pearson coefficients of 0.69 for range and 0.82 for ADRR (P<0.0001 for both).

**Subgroup Analyses**

There was a significant interaction between mean BG category (<110 mg/dL, 110 to <140 mg/dL, 140 to <170
### Table 1. Baseline Characteristics of Patients Admitted for Acute Myocardial Infarction Who Had at Least 3 Blood Glucose Measures During the First 48 Hours of Hospitalization Stratified by Quartiles of Range

<table>
<thead>
<tr>
<th>Glucose Variability (Range, mg/dl)</th>
<th>Quartile 1 (0 to &lt;31)</th>
<th>Quartile 2 (31 to &lt;64)</th>
<th>Quartile 3 (64 to &lt;127)</th>
<th>Quartile 4 (127 to 917)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age, y</td>
<td>68.1 ± 14.9</td>
<td>70.0 ± 14.2</td>
<td>70.3 ± 13.3</td>
<td>70.0 ± 12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race category</td>
<td></td>
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</tr>
<tr>
<td>White, %</td>
<td>3773 (84.7%)</td>
<td>4202 (87.4%)</td>
<td>3931 (84.8%)</td>
<td>3857 (82.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>425 (9.5%)</td>
<td>371 (7.7%)</td>
<td>399 (8.6%)</td>
<td>494 (10.6%)</td>
<td>0.108</td>
</tr>
<tr>
<td>Other, %</td>
<td>259 (5.8%)</td>
<td>233 (4.8%)</td>
<td>303 (6.5%)</td>
<td>316 (6.8%)</td>
<td>0.376</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>1727 (38.7%)</td>
<td>1970 (41.0%)</td>
<td>1995 (43.1%)</td>
<td>2307 (49.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Clinical characteristics, %</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1320 (29.6%)</td>
<td>1748 (36.4%)</td>
<td>2013 (43.4%)</td>
<td>2489 (53.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2451 (55.0%)</td>
<td>2588 (53.8%)</td>
<td>2759 (55.7%)</td>
<td>2363 (50.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>150 (3.4%)</td>
<td>175 (3.6%)</td>
<td>148 (3.2%)</td>
<td>184 (3.9%)</td>
<td>0.293</td>
</tr>
<tr>
<td>PVD</td>
<td>149 (3.3%)</td>
<td>146 (3.0%)</td>
<td>126 (2.7%)</td>
<td>122 (2.6%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Dementia</td>
<td>86 (1.9%)</td>
<td>98 (2.0%)</td>
<td>86 (1.9%)</td>
<td>68 (1.5%)</td>
<td>0.066</td>
</tr>
<tr>
<td>Lung disease</td>
<td>591 (13.3%)</td>
<td>709 (14.8%)</td>
<td>769 (16.6%)</td>
<td>791 (16.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>450 (10.1%)</td>
<td>1074 (22.4%)</td>
<td>2163 (46.7%)</td>
<td>3376 (72.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI</td>
<td>1711 (38.4%)</td>
<td>1877 (39.1%)</td>
<td>1744 (37.6%)</td>
<td>1440 (30.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>In hospital procedures, %</strong></td>
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</tr>
<tr>
<td>Coronary Angiography</td>
<td>3035 (68.1%)</td>
<td>3001 (62.4%)</td>
<td>2838 (61.3%)</td>
<td>2579 (55.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In hospital PCI</td>
<td>1913 (42.9%)</td>
<td>1908 (39.7%)</td>
<td>1564 (33.8%)</td>
<td>1390 (29.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In hospital CABG</td>
<td>516 (11.6%)</td>
<td>566 (11.8%)</td>
<td>748 (16.1%)</td>
<td>604 (12.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Admission lab values</strong></td>
<td></td>
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<tr>
<td>Creatinine, mg/dl</td>
<td>1.3 ± 1.0</td>
<td>1.5 ± 1.2</td>
<td>1.5 ± 1.3</td>
<td>1.7 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39.5 ± 5.8</td>
<td>39.0 ± 6.3</td>
<td>38.8 ± 6.3</td>
<td>37.7 ± 6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC count, 10^9/μL</td>
<td>10.3 ± 4.9</td>
<td>10.8 ± 4.8</td>
<td>11.6 ± 7.9</td>
<td>12.4 ± 11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak troponin, ng/mL</td>
<td>276 ± 59.0</td>
<td>319 ± 64.7</td>
<td>319 ± 66.7</td>
<td>303 ± 65.0</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Blood glucose measures</strong></td>
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<tr>
<td>First glucose, mg/dl</td>
<td>118.2 ± 23.3</td>
<td>141.2 ± 34.7</td>
<td>177.3 ± 56.4</td>
<td>274.0 ± 128.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean glucose (1st 48 h), mg/dl</td>
<td>115.0 ± 22.4</td>
<td>131.3 ± 30.3</td>
<td>158.3 ± 42.1</td>
<td>209.2 ± 65.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of glucose measures in 1st 48 h Median [Q1, Q3]</td>
<td>3.0 (3.0, 3.0)</td>
<td>3.0 (3.0, 4.0)</td>
<td>4.0 (3.0, 7.0)</td>
<td>6.0 (3.0, 11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Length of stay</strong></td>
<td></td>
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<tr>
<td>Length of stay, hours</td>
<td>153.2 ± 106.1</td>
<td>163.9 ± 112.3</td>
<td>178.0 ± 119.4</td>
<td>195.7 ± 132.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>In hospital medications, %</strong></td>
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</tr>
<tr>
<td>Insulin</td>
<td>523 (11.7%)</td>
<td>945 (19.7%)</td>
<td>1837 (39.7%)</td>
<td>2926 (62.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral antihyperglycemic drugs</td>
<td>174 (3.9%)</td>
<td>508 (10.6%)</td>
<td>1134 (24.5%)</td>
<td>1550 (33.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3844 (86.2%)</td>
<td>4127 (85.9%)</td>
<td>3952 (85.3%)</td>
<td>3903 (83.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>2746 (61.6%)</td>
<td>2921 (60.8%)</td>
<td>2649 (57.2%)</td>
<td>2512 (53.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>3796 (85.2%)</td>
<td>4104 (85.4%)</td>
<td>3974 (85.8%)</td>
<td>3858 (82.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>986 (22.1%)</td>
<td>1161 (24.2%)</td>
<td>1285 (27.7%)</td>
<td>1363 (29.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2104 (47.2%)</td>
<td>2583 (53.8%)</td>
<td>2851 (61.6%)</td>
<td>3121 (66.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrites</td>
<td>3248 (72.9%)</td>
<td>3550 (73.9%)</td>
<td>3361 (72.6%)</td>
<td>3413 (73.1%)</td>
<td>0.834</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>874 (19.6%)</td>
<td>1086 (22.6%)</td>
<td>1354 (29.2%)</td>
<td>1410 (30.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>2697 (60.5%)</td>
<td>2855 (59.4%)</td>
<td>2845 (61.4%)</td>
<td>2773 (59.4%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>302 (6.8%)</td>
<td>315 (6.6%)</td>
<td>372 (8.0%)</td>
<td>434 (9.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>2983 (66.9%)</td>
<td>3105 (64.6%)</td>
<td>2991 (64.6%)</td>
<td>2918 (62.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

y indicates years; TIA, transient ischemic attack; PVD, peripheral vascular disease; STEMI, ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; WBC, white blood cells; ACE, angiotensin-converting enzyme.
mg/dL, 170 to <200 mg/dL, and ≥200 mg/dL) and GV metrics (range and ADRR modeled as continuous variables; \( P < 0.0001 \) for each) in unadjusted models. In the fully adjusted analyses, the interaction probability values were attenuated at 0.01 for range and 0.06 for ADRR. In these fully adjusted models, range as a continuous variable was independently predictive of inpatient mortality only in the lowest mean BG category (≤110 mg/dL) while ADRR was not. Range as a categorical variable (in quartiles) was no longer significant within this lowest mean BG category. Unadjusted and adjusted mortality rates across categories of mean BG and range are depicted in Figure 2.

The interaction probability values between STEMI status and GV metrics were significant for SD, range, ADRR, and MAG, but not for mean amplitude of glucose excursions. In analyses stratified by STEMI versus NSTEMI status, odds ratios (OR) for mortality were increased in patients with STEMI for SD (OR per 10-point increase in SD, 1.03; 95% CI, 1.00 to 1.07), range (OR per 10-point increase in range, 1.03; 95% CI, 1.01 to 1.04), and MAG (OR per 10-point increase in MAG, 1.28; 95% CI, 1.08 to 1.52), but not for ADRR; whereas the ORs for mortality were not significantly increased for any of GV metrics in patients with NSTEMI. After full adjustment, ORs for mortality remained elevated in patients with STEMI for range (OR, 1.02; 95% CI, 1.00 to 1.03) and MAG (OR, 1.32; 95% CI, 1.07 to 1.62), but not for other GV metrics.

There were no significant interactions by diabetes status or insulin use during hospitalization in fully adjusted models.

### Sensitivity Analysis

When analysis was limited to patients with at least 6 BG values during the first 48 hours of hospitalization, results similarly showed that none of the GV metrics were independent predictors of mortality after adjustment (mean amplitude of glucose excursions no longer significant in unadjusted models).
models, ADRR and MAG in models adjusted for mean BG, while SD and range in fully adjusted models).

Discussion

In this large cohort of patients hospitalized with AMI, we demonstrate that, although GV is associated with crude in-hospital mortality, none of the GV metrics remained significantly associated with mortality after multivariable adjustment in our primary analysis. Specifically, GV derived from routinely collected BG data does not offer a significant, incremental advantage in the ability to predict mortality compared with mean BG alone. In contrast, mean BG remains an independent predictor of in-hospital death, even in models adjusting for GV and multiple patient characteristics.

In contrast to our findings, multiple studies from the intensive care unit setting have shown a strong relationship between GV and mortality.\textsuperscript{13–18,20–22} Critically ill patients with wide glycemic variations appear to be at significantly higher risk for death, whether they are hospitalized in medical, surgical, pediatric, trauma, or burn units. Adjustment for demographic and clinical characteristics attenuates these relationships to a modest degree in prior studies. Few studies specifically accounted for the impact of hypoglycemia\textsuperscript{13,15,21} on the relationship between GV and outcomes. Four studies have shown that this association is independent of mean BG\textsuperscript{13,16–18}; however, owing to treatment protocols in place in most of the units, the distribution of mean BG was small in these studies.

There are several possible explanations for the differences in these prior studies as compared with our findings in AMI. Conceivably, critically ill patients may be particularly susceptible to deleterious effects of fluctuating glucose levels, more so than patients admitted for AMI. It is also possible that our dataset contains more detailed information on potential confounders. For example, only half of the prior studies included a severity-of–illness indicator in their models,\textsuperscript{13,15–18,31} and few contained detailed data on comorbidities. In addition, there is no single established measure of GV, and prior studies have tested and reported on a variety of such measures. As suggested by a recent systematic review, reporting bias may result in GV measures found to be more strongly associated with outcomes to be preferentially reported and published.\textsuperscript{31}

Another possibility is that the intensity of BG monitoring (and therefore the amount of data that is used to measure GV) may differ between critically ill patients in medical and surgical intensive care units and those with AMI. BG moni-
toring tends to be more frequent in medical/surgical intensive care units versus coronary care units. For example, Hermanides et al used a median of 11 blood glucose values per day to calculate GV. This frequency reflects widespread adoption of intensive insulin treatment protocols that rely on BG measures obtained every 1 to 2 hours. In contrast, our data were based on routinely collected glucose measures in the setting of AMI, where targeted glucose control protocols are rarely used, and hourly blood glucose measures are infrequently performed. In our study, patients had a median of 3 BG measures during the first 48 hours of hospitalization. This relatively small number of measurements means that a single extreme BG value may affect both the mean and the variability, potentially resulting in the strong correlation between the 2 measures. Conceivably, greater number of BG measures may overcome these limitations and improve the accuracy of the GV metrics, although our sensitivity analyses using a minimum of 6 BG values did not support this hypothesis.

One prior study evaluated the role of variation in BG levels on outcomes of patients with AMI. The metric examined in the study was the difference between admission blood glucose and the lowest fasting glucose recorded during hospitalization. Analyses showed that this metric was associated with long-term but not in-hospital outcomes, including mortality; however, results were adjusted for neither admission nor mean BG; therefore, it remains unclear whether this metric is independently associated with patient outcomes.

Whether GV directly contributes to increased mortality or whether it is simply a marker for degree of critical illness is unknown. The underlying mechanisms for the adverse effects of GV on patient outcomes have been proposed to involve oxidative stress, release of inflammatory cytokines, and endothelial dysfunction. At the same time, patients with higher GV tend to have more comorbidities and greater severity of illness. Changes in stress response, treatment strategies (for example, corticosteroids), and organ dysfunction (for example, liver) can all contribute to both hypoglycemia and hyperglycemia, with rapid fluctuations in glucose levels. Our study suggests that GV may be a marker for sicker patients, as we found that patients with more comorbidities and greater acuity of illness at presentation had higher levels of GV. Importantly, adjustment for patient factors, including mean BG, renders GV no longer a significant independent predictor of mortality in our primary multivariable models.

Although, in the overall sample, there was no significant independent association between GV and mortality, we explored whether such an association may exist in specific subgroups of mean BG. In stratified analyses, we found that higher range is significantly associated with mortality in patients with lowest mean BG, even in fully adjusted models; however, these findings were not significant for ADRR or other GV metrics. Moreover, the interactions between mean BG and these GV metrics were highly attenuated in fully adjusted models, suggesting that confounders may largely explain these interactions. Prior work by Ali et al showed that glucose lability index (a measure of GV) was independently associated with mortality in septic patients with lower mean BG values (below the median). Although these findings are interesting, their clinical applicability remains unclear, and they will need to be confirmed in future studies.

In addition, subgroup analyses by STEMI versus NSTEMI status showed that higher GV (for 2 of the metrics) was associated with significantly increased mortality risk in patients with STEMI but not in patients with NSTEMI. Prior work showed that the relationship between glycemia and mortality is similar in patients with STEMI and NSTEMI; however, specific evaluation of the impact of STEMI status on GV has not been previously undertaken. Whether GV plays a special role in patients with STEMI or whether it is simply a prognostic marker remains unclear, and the association between GV and outcomes in patients with STEMI will need to be replicated in future studies.

Our findings should be interpreted in the context of the following potential limitations. As already mentioned, we relied on BG data routinely collected during clinical practice to calculate our GV metrics; therefore, the number and the timing of BG measures were variable between patients. By necessity, we also had to exclude a large number of patients who did not have at least 3 BG values obtained during 48 hours; thus, limiting the generalizability of our findings unless those who are included are generally representative of all patients with AMI.

We evaluated 5 different GV metrics in multiple models and subgroups. Our analyses were not adjusted for multiple comparisons; our overall negative findings, with a more liberal threshold for describing statistical significance, minimize this concern, but our subgroup analyses should be interpreted with caution. In addition, we could not investigate the impact of GV on other end points, such as cardiac arrhythmia, or long-term outcomes. Finally, our results are not generalizable to patients with non-AMI.

In conclusion, GV calculated using clinical data during the initial 48 hours of hospitalization does not independently predict in-hospital mortality in patients admitted for AMI after adjustment for multiple patient factors, including mean BG. Our study suggests that using GV calculated from clinically obtained BG values (in addition to mean BG) for risk stratification may not be warranted in patients with AMI, and intervention efforts specifically aimed at GV-lowering appear premature in this patient group. Future studies should specifically explore the impact of GV on outcomes in patients with STEMI and in those with low mean BG values. However, these studies should not assess GV using clinical data in this patient population given the scarcity of glucose values obtained during AMI; rather, the role of GV should be further investigated in clinical studies where frequent BG values are systematically and frequently collected.

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References


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