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CORRESPONDENCE

Research Correspondence

U-Shaped Relationship of Blood Glucose With Adverse Outcomes Among Patients With ST-Segment Elevation Myocardial Infarction

To the Editor: Hyperglycemia, with or without pre-existing diabetes mellitus, is associated with adverse outcomes in patients with acute coronary syndromes (1). Whereas blood glucose levels (BGLs) ≥200 mg/dl are associated with adverse outcomes after acute myocardial infarction (AMI), the association of moderate elevations or hypoglycemia with cardiovascular mortality in ST-segment elevation myocardial infarction (STEMI) patients is not well characterized. We hypothesized that both hypoglycemia and moderate elevations of the BGL during STEMI would be associated with increased rates of adverse outcomes, irrespective of diabetic status.

Clinical data in STEMI patients were pooled from the Thrombolysis In Myocardial Infarction (TIMI)-10A/B, Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction (LIMIT-AMI), and Optimal Angioplasty versus Primary Stenting (OPUS)–TIMI-16 studies (n = 4,224). The trial designs have been previously described. Angiographic data (n = 1,260) were available from all trials except OPUS–TIMI-16. We divided all patients into six groups based on the BGL. Previous studies have focused on severe hyperglycemia (BGL > 199 mg/dl), so previously described (2) definitions of impaired glucose tolerance (BGL 100 to 125 mg/dl, n = 1,229) and diabetes (BGL ≥126 mg/dl) were used. To determine whether risk increased in parallel with increasingly severe hyperglycemia, patients with a BGL ≥126 mg/dl were arbitrarily divided into mild (BGL 126 to 149 mg/dl; n = 792), moderate (BGL 150 to 199 mg/dl; n = 702) and severe (BGL >199 mg/dl; n = 598) hyperglycemia. Hypoglycemia was defined as a BGL <81 mg/dl (n = 325). A BGL of 81 to 99 mg/dl represented euglycemia (n = 578). Admission BGLs were drawn except in the OPUS–TIMI-16 study, where BGLs were drawn <48 h from admission. Individual and combined end points of death or recurrent myocardial infarction were analyzed at 30-day follow-up.

Analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas) or higher. Continuous variable values are reported as the mean ± SD or median with 25% and 75% confidence intervals. Continuous variables were analyzed using the Student *t* test for two-way comparisons and analysis of variance for >2-way comparisons. The chi-square test was used to analyze categorical variables. A multivariate logistic regression model for mortality at 30 days was generated using BGLs of 81 to 99 mg/dl as the referent group.

Compared with euglycemia, patients with hypoglycemia had lower body weight and were more often diabetic. Compared with euglycemia, patients with hyperglycemia were older, with higher heart rates, prevalence of hypertension, congestive heart failure (CHF), and diabetes, but less tobacco use. Patients with a previous diagnosis of diabetes accounted for 17.5% of all patients, but they accounted for 69.4% of patients with a BGL >199 mg/dl. A BGL ≥126 mg/dl was present in ~50% of patients without a diagnosis of diabetes.

Higher BGL was associated with a higher TIMI risk score (TRS) for STEMI and TIMI risk index. Higher TIMI risk indexes were noted among hyperglycemic but not hypoglycemic diabetics. Angiographic measures of epicardial flow, myocardial perfusion, extent of coronary disease, and infarct location were not significantly associated with BGL.

There was a U-shaped relationship between BGL and adverse outcomes. Death occurred in 4.6% of patients with a BGL ≤81 mg/dl, 4.7% of those with a BGL >199 mg/dl, and 1.0% of those with euglycemia ($p < 0.001$). Recurrent MI or death occurred in 10.5% of patients with a BGL <81 mg/dl, 7.2% of those with a BGL >199 mg/dl, and 4.2% of those with euglycemia ($p < 0.001$) (Fig. 1A).

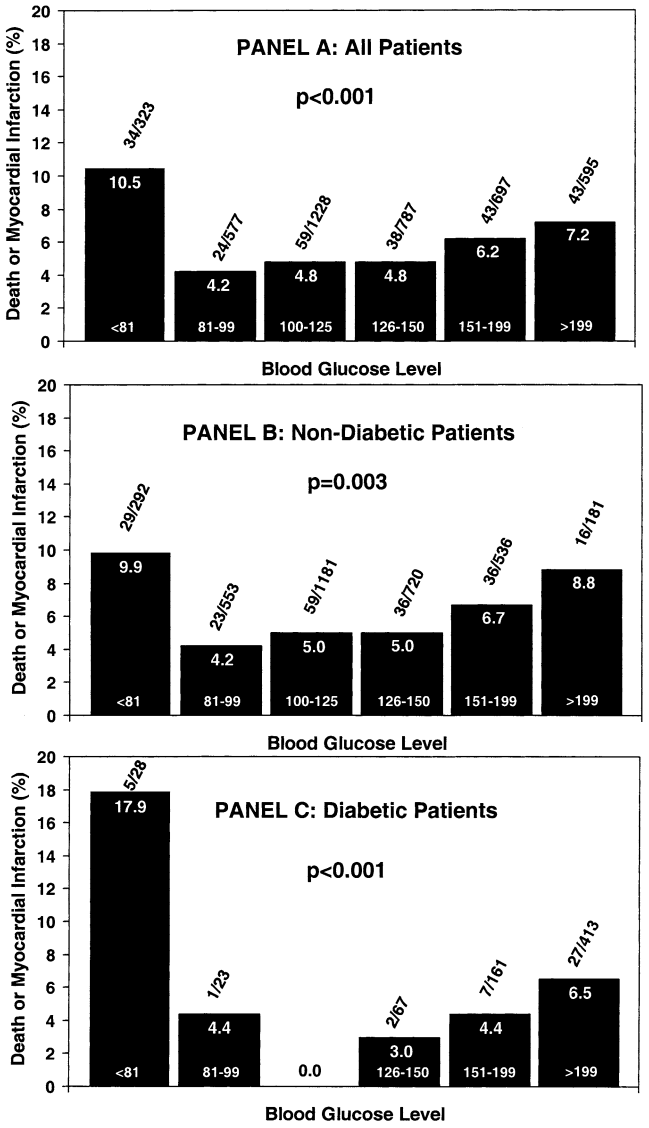

Figure 1. U-shaped association of admission blood glucose level with death or recurrent myocardial infarction at 30 days in the overall population (n = 4,227) **(A),** nondiabetic patients (n = 3,463) **(B),** and diabetic patients (n = 738) **(C)**.

Stratification according to the presence or absence of a previous diagnosis of diabetes showed that, without diabetes, the combined end point of death or recurrent MI was significantly associated with BGL ($p = 0.003$; Fig. 1B), and with diabetes there were significant differences in 30-day mortality ($p = 0.001$) and recurrent death or MI rates (Fig. 1C) in strata of BGL ($p < 0.0001$). No significant statistical interaction was identified between BGLs <81 mg/dl or BGLs >199 mg/dl and a history of diabetes ($p = 0.20$ and $p = 0.23$, respectively).

Among those with a TRS >4, a U-shaped relationship was seen between 30-day mortality and BGL ($p < 0.001$). Those with both hypoglycemia and TRS >4 had ~10-fold higher mortality compared with a similar TRS and euglycemia (22.6% vs. 2.5%; $p < 0.01$) (Fig. 2). A significant interaction between hypoglycemia and the TRS was found (odds ratio [OR] 11.2, 95% confidence interval [CI] 1.2 to 99.8; $p = 0.03$). Modest increases in BGLs were associated with increased mortality in patients with the highest TRS ($p < 0.01$). Those with a low (0 to 2) or medium (3 to 4) TRS showed a monotonic rise in adverse outcomes with increasing BGL.

A multivariate logistic regression model using a BGL of 81 to 99 mg/dl as the referent group adjusted for differences among the six groups including age, gender, weight, blood pressure, pulse, race, smoking status, prior MI, history of hypertension, history of diabetes, and Killip class. A BGL <81 mg/dl remained associated with increased mortality (OR 3.37, 95% CI 1.23 to 9.22, $p = 0.018$), as did a BGL of 150 to 199 mg/dl (OR 2.93, 95% CI 1.17 to 7.33, $p = 0.021$), and BGLs >199 mg/dl (OR 3.09, 95% CI 1.15 to 8.31, $p = 0.026$). Mortality was slightly but not significantly increased with a BGL of 100 to 125 mg/dl and 126 to 149 mg/dl. Delays in obtaining BGLs during the OPUS–TIMI-16 trial likely did not influence these findings because the association of low and high BGL with adverse outcomes persisted after adjustment for the time from symptom onset to randomization and after data from this OPUS–TIMI-16 study were excluded.

This study builds on previous reports that associate marked hyperglycemia with mortality (3), by demonstrating an exceptionally poor prognosis with hypoglycemia and milder elevations of BGLs after STEMI, irrespective of a history of diabetes. The stepwise increase in adverse events associated with moderate BGL elevations further validates the clinical importance of impaired glucose tolerance and diabetes. The high prevalence of dysglycemia in nondiabetic patients shows many STEMI patients to be at risk. A similar risk of mortality at one year is noted among diabetic patients and those newly diagnosed with diabetes during MI (4). The diagnosis of diabetes, however, during MI is often difficult, and diabetes cannot be confirmed, when World Health Organization guidelines for diagnosis are applied, in over 50% of patients who initially present with a BGL >200 mg/dl at the time of infarction (5,6). Blood glucose level was associated with adverse outcomes independent of prior diabetic status, highlighting the need for increased recognition of elevated risk among patients with impaired glucose metabolism, regardless of whether diabetes has been diagnosed.

Those with a BGL <81 mg/dl represented only 8% of all patients with STEMI, but accounted for 13% of all deaths; however, little is known regarding the association between hypoglycemia and outcomes in STEMI (7). Patients with both an elevated TRS and hypoglycemia had a 10-fold increased mortality when compared to those who were euglycemic. Hypoglycemia was unlikely from medications in this study because only 8.7% of the hypoglycemic group carried a diagnosis of diabetes, making use of hypoglycemics improbable in the majority of patients. Hypoglycemic patients may have had hepatic synthetic dysfunction due to unrecognized disease but acute hepatic congestion from cardiogenic shock was unlikely because shock was an exclusion criterion in these trials, and multivariate analysis did not show any relationship between hemodynamic variables and outcome. Alcoholism or adrenal insufficiency may have contributed but was not ascertained. The extent of coronary disease or efficacy of reperfusion did not

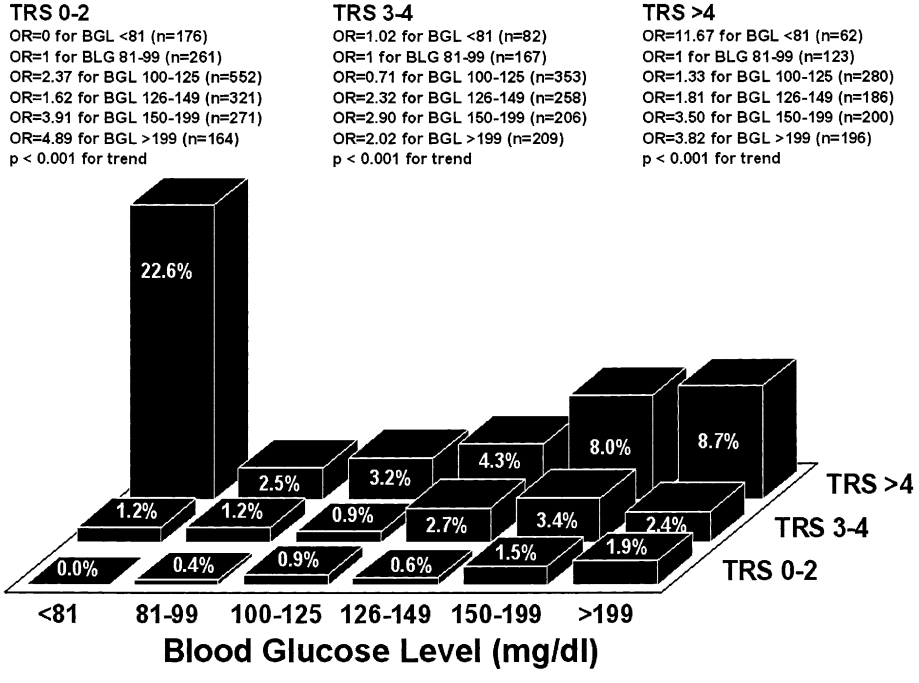

Figure 2. Relationship of blood glucose level (BGL) and death at 30 days stratified by Thrombolysis In Myocardial Infarction (TIMI) risk score (TRS). OR = odds ratio.

explain these findings because these were similar between the groups.

Current risk stratification scores do not use BGL as a prognostic variable. Our findings demonstrate a two- to four-fold increased risk of death with high or low BGL after STEMI, highlighting an additive prognostic value to such models. Specifically, a BGL <81 mg/dl was associated with a 3-fold increased risk of death at 30 days ($p = 0.01$), whereas hypoglycemic patients with a TRS >4, had a >11-fold increased risk of death.

Although the Diabetic Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)-2 trial showed no advantage for intensive glucose management (8), a need to identify high-risk patients with abnormal glucose metabolism remains. The negative results may reflect improved overall management of patients identified as high-risk. The effect of treating BGL abnormalities was not assessed in this study, but an understanding of the mechanisms leading to adverse outcomes with mild hyperglycemia or hypoglycemia in the STEMI population could perhaps lead to novel metabolic therapies to improve outcomes.

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Letters to the Editor

Frequency of Cardiac Troponin I Mutations in Families With Hypertrophic Cardiomyopathy in China

I read with interest the recent study on the frequency of cardiac troponin I (cTnI) mutations in families with hypertrophic cardiomyopathy (HCM) reported from the United Kingdom (1). It is amazing to note that the prevalence of cTnI mutations in the United Kingdom (3.1%) is almost identical to that in China (3%) (2).

My colleagues from Nanjing (formerly Nanking), China (2), studied 71 patients with HCM, 45 male and 26 female, ranging in age from 10 to 77 years (average age, 45.5 ± 17.2 years). Exons 7 and 8 of cTnI gene of the 71 patients and 100 normal controls were amplified by polymerase chain reaction (PCR), and the products of PCR were analyzed by direct sequencing. Two mutations of cTnI were identified in 71 patients with HCM (3%) but not in the normal controls. Pedigree investigation showed another carrier in each family: the cTnIR145W mutation carrier had no clinical abnormalities, and the cTnIR162Q carrier had atrial fibrillation when he was in his 20s. Further animal work using recombinant cTnIR145W transduction into cultured mouse adult cardiomyocytes is in progress (2).

Therefore, as Maron (3) recently noted, HCM is indeed an important global disease. Not only is the prevalence of HCM in China (0.16%) (4,5) almost the same as in the Western world (0.2%, according to the Coronary Artery Risk Development In Young Adults [CARDIA] study [6]), but the frequency rates of cTnI mutations are the same (3%) (1,2). This low frequency is consistent with that reported from other countries (<5%) (5,7).

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