# Fasting Glucose in Acute Myocardial Infarction

## Incremental value for long-term mortality and relationship with left ventricular systolic function

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**OBJECTIVE** — Elevation of blood glucose is a common metabolic disorder among patients with acute myocardial infarction (AMI) and is associated with adverse prognosis. However, few data are available concerning the long-term prognostic value of elevated fasting glucose during the acute phase of infarction.

**RESEARCH DESIGN AND METHODS** — We prospectively studied the relationship between fasting glucose and long-term mortality in patients with AMI. Fasting glucose was determined after an ≥8 h fast within 24 h of admission. The median duration of follow-up was 24 months (range 6–48). All multivariable Cox models were adjusted for the Global Registry of Acute Coronary Events (GRACE) risk score.

**RESULTS** — In nondiabetic patients ($n$ = 1,101), compared with patients with normal fasting glucose (<100 mg/dl), the adjusted hazard ratio for mortality progressively increased with higher tertiles of elevated fasting glucose (first tertile 1.5 [95% CI 0.8–2.9], $P$ = 0.19; second tertile 3.2 [1.9–5.5], $P < 0.0001$; third tertile 5.7 [3.5–9.3], $P < 0.0001$). The $c$ statistic of the model containing the GRACE risk score increased when fasting glucose data were added (0.8 ± 0.02–0.85 ± 0.02, $P$ = 0.004). Fasting glucose remained an independent predictor of mortality after further adjustment for ejection fraction. Elevated fasting glucose did not predict mortality in patients with diabetes ($n$ = 462).

**CONCLUSIONS** — Fasting glucose is a simple robust tool for predicting long-term mortality in nondiabetic patients with AMI. Fasting glucose provides incremental prognostic information when added to the GRACE risk score and left ventricular ejection fraction. Fasting glucose is not a useful prognostic marker in patients with diabetes.

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Recent studies have emphasized the prognostic value of high blood glucose levels in patients with acute myocardial infarction (AMI) (1–6). Previous investigations focused on the relationship between random blood glucose on admission and outcome. We have previously shown that elevated fasting glucose concentrations are superior to admission glucose levels in predicting 30-day mortality in patients with AMI (7). However, few data on the relationship between fasting glucose and long-term outcome are available.

Knowledge of mortality predictors in AMI can be used to generate predictive models that can aid clinicians' decisions making, in particular in identifying patients who are at high or low risk of death (8). Such risk assessment methods have been developed for acute coronary syndromes (9–11). Whether glucose levels can be used to improve the predictive ability of such risk models is not known.

Heart failure has been shown to promote insulin resistance and glucose intolerance (12,13), raising the possibility that the association between stress hyperglycemia and adverse outcome is partly mediated through the acute reduction in left ventricular systolic performance. However, the relationship between infarct size or left ventricular dysfunction and the degree of stress hyperglycemia remains controversial (14–18).

In the present study, we prospectively evaluated the long-term predictive value of fasting glucose in patients with AMI. Our study had the following three aims: *1*) to ascertain the predictive ability of fasting glucose for long-term mortality after myocardial infarction, *2*) to determine the incremental predictive value of fasting glucose for long-term mortality over an established risk score, and *3*) to clarify the relationship between stress hyperglycemia and left ventricular systolic fraction.

## RESEARCH DESIGN AND METHODS

— The study included patients presenting to the intensive coronary care unit of Rambam Medical Center with AMI between July 2001 and June 2005. AMI was diagnosed on the basis of the European Society of Cardiology and American College of Cardiology criteria (19). Exclusion criteria were admission at >24 h from symptom onset, known inflammatory disease, and surgery or trauma within the previous month. The investigational review committee on human research approved the study protocol.

### Plasma glucose measurements

Blood samples for fasting glucose were obtained after an overnight fast of at least 8 h, within 24 h of admission. Intravenous glucose solutions were not allowed, but adrenergic agents were used if clini-

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**Abbreviations:** AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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**Table 1—*Baseline clinical characteristics of the study groups***

| Characteristic | Normal fasting glucose (< 100 mg/dl) | Tertiles of elevated fasting glucose* | | | Diabetes | $P_{trend}$ |
|---|---|---|---|---|---|---|
| | | First (100–111 mg/dl) | Second (112–129 mg/dl) | Third (≥130 mg/dl) | | |
| *n* | 442 | 218 | 219 | 222 | 462 | |
| Age (years) | 59 ± 13 | 64 ± 11 | 63 ± 14 | 62 ± 14 | 66 ± 13 | 0.006 |
| Men | 369 (84) | 184 (84) | 168 (77) | 163 (73) | 317 (69) | <0.0001 |
| Previous infarct | 83 (19) | 46 (21) | 37 (17) | 53 (24) | 134 (29) | <0.0001 |
| Previous heart failure | 17 (4) | 5 (2) | 7 (3) | 13 (6) | 41 (9) | <0.0001 |
| Current smoking | 63 (14) | 34 (16) | 30 (14) | 37 (17) | 90 (20) | 0.03 |
| History of hypertension | 200 (45) | 95 (44) | 103 (47) | 138 (63) | 305 (66) | <0.0001 |
| Creatinine (mg/dl) | 1.0 ± 0.5 | 1.1 ± 0.6 | 1.0 ± 0.4 | 1.2 ± 0.8 | 1.2 ± 1.1 | 0.008 |
| LDL cholesterol (mg/dl) | 114 ± 39 | 126 ± 27 | 135 ± 29 | 133 ± 27 | 130 ± 42 | 0.82 |
| HDL cholesterol (mg/dl) | 43.5 ± 10.7 | 4.3 ± 11.2 | 42.7 ± 7.2 | 42.9 ± 7.3 | 39.3 | 0.35 |
| Triglycerides (mg/dl) | 142 ± 75 | 168 ± 79 | 170 ± 54 | 163 ± 77 | 216 ± 166 | 0.02 |
| BMI (kg/m$^2$) | 26.7 ± 3.9 | 26.8 ± 4.3 | 27.7 ± 3.9 | 27.4 ± 4.6 | 28.3 ± 4.6 | 0.001 |
| Systolic blood pressure at admission (mmHg) | 130 ± 24 | 133 ± 29 | 133 ± 27 | 130 ± 28 | 127 ± 37 | 0.31 |
| Heart rate at admission (beats/min) | 75 ± 17 | 83 ± 18 | 76 ± 18 | 76 ± 20 | 87 ± 19 | 0.001 |
| Killip class at admission | 1.2 ± 0.6 | 1.6 ± 0.6 | 1.4 ± 0.8 | 1.5 ± 0.9 | 2.0 ± 1.2 | <0.0001 |
| ST elevation infarction | 297 (67) | 156 (72) | 168 (77) | 179 (81) | 306 (66) | 0.73 |
| Anterior infarction | 174 (39) | 103 (47) | 95 (43) | 111 (50) | 204 (44) | 0.12 |
| Thrombolytic therapy | 109 (25) | 51 (23) | 58 (27) | 44 (20) | 80 (17) | 0.004 |
| Primary angioplasty | 108 (24) | 54 (25) | 54 (25) | 70 (32) | 97 (21) | 0.54 |
| Coronary revascularization† | 116 (38) | 90 (41) | 85 (39) | 84 (38) | 130 (28) | 0.002 |
| Ejection fraction (%) | 49 ± 11 | 47 ± 12 | 45 ± 12 | 40 ± 13 | 43 ± 13 | <0.0001 |
| Medical therapies | | | | | | |
| Aspirin | 438 (99) | 215 (99) | 207 (95) | 195 (88) | 444 (96) | <0.0001 |
| β-Blockers | 373 (84) | 188 (86) | 172 (79) | 140 (63) | 377 (82) | 0.003 |
| ACE inhibitors/ARBs | 347 (79) | 179 (82) | 161 (34) | 144 (65) | 377 (82) | 0.74 |
| Statins | 299 (68) | 159 (73) | 132 (60) | 119 (54) | 312 (68) | 0.16 |

Data are *n* (%) or means ± SD. Trends for categorical variables were calculated with the use of the Cochran-Armitage trend test. *To convert from milligrams per deciliter to millimoles per liter, multiply plasma glucose values by 0.0555. †Percutaneous coronary intervention or coronary artery bypass graft surgery during hospital stay. ARB, angiotensin II receptor blocker.

cally indicated. Plasma glucose was enzymatically determined with the glucose oxidase method using an AutoAnalyzer (Hitachi, Tokyo, Japan).

### Assessment of left ventricular systolic function

Echocardiography was performed during the hospital stay after a median of 2 days from admission (interquartile range 1–3 days). Analysis of left ventricular ejection fraction (LVEF) was carried out by echocardiography. LVEF was classified as normal (≥55%), mildly reduced (45–54%), moderately reduced (30–44%), and severely reduced (<30%) (20).

### Study end points and definitions

Patients were considered to have diabetes if they had been previously informed of the diagnosis by a physician, were taking oral antihyperglycemic agents or insulin, or were receiving diet therapy. Classification of normal fasting glucose and admission glucose levels was made prospectively according to the recent criteria of the American Diabetes Association (21). Patients were classified as having normal fasting glucose using a cutoff level of <100 mg/dl. Patients with elevated fasting glucose levels were divided into tertiles of elevated fasting glucose. Patients were classified as having normal admission (random) plasma glucose using a cutoff level of <140 mg/dl, and patients with elevated admission levels were divided into tertiles of elevated admission glucose values.

The primary end point of the study was all-cause mortality. After discharge from the hospital, clinical end point information was acquired by reviewing the national death registry and by contacting each patient individually.

### Statistical analysis

The baseline characteristics of group categorized by fasting glucose levels were compared using ANOVA for continuous variables and by the $\chi^2$ statistic for categorical variables. The relation between median glucose levels across categories of LVEF was assessed using the nonparametric Jonckheere-Terpstra test.

Event-free survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs for various admission and fasting glucose categories after adjustment for the Global Registry of Acute Coronary Events (GRACE) risk score (10). The GRACE risk score is a validated nine-variable prediction tool that can be used to estimate a patient's risk for all-cause mortality in the

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**Table 2—*Unadjusted and adjusted Cox proportional hazards models for long-term mortality according to categories of admission and fasting glucose in patients without diabetes****

| Glucose categories† | *n* | Events (%) | Unadjusted OR (95% CI) | *P* value | $P_{trend}$ | Adjusted OR (95% CI) | *P* value | $P_{trend}$ |
|---|---|---|---|---|---|---|---|---|
| Model 1: admission glucose‡ | | | | | <0.0001 | | | <0.0001 |
| Normal (<140 mg/dl) | 672 | 64 (9.5) | 1.0 | | | 1.0 | | |
| Elevated, first tertile (141–180 mg/dl) | 159 | 20 (12.6) | 1.3 (0.8–2.2) | 0.28 | | 1.1 (0.7–1.9) | 0.26 | |
| Elevated, second tertile (181–230 mg/dl) | 131 | 26 (19.8) | 2.2 (1.4–3.4) | 0.0008 | | 1.9 (1.2–2.9) | 0.009 | |
| Elevated, third tertile (≥230 mg/dl) | 139 | 60 (43.2) | 5.7 (4.0–8.1) | <0.0001 | | 3.8 (2.7–5.4) | <0.0001 | |
| Model 2: fasting glucose§ | | | | | <0.0001 | | | <0.0001 |
| Normal (<100 mg/dl) | 442 | 28 (6.3) | 1.0 | | | 1.0 | | |
| Elevated, first tertile (100–110 mg/dl) | 218 | 19 (8.7) | 1.4 (0.8–2.5) | 0.26 | | 1.5 (0.8–2.9) | 0.19 | |
| Elevated, second tertile (112–129 mg/dl) | 219 | 39 (17.8) | 3.0 (1.9–4.9) | <0.0001 | | 3.2 (1.9–5.5) | <0.0001 | |
| Elevated, third tertile (≥130 mg/dl) | 222 | 84 (37.8) | 7.4 (4.8–11.3) | <0.0001 | | 5.7 (3.5–9.3) | <0.0001 | |
| Model 3: Fasting glucose + diabetes‖ | | | | | <0.0001 | | | <0.0001 |
| Normal (<100 mg/dl) | 442 | 28 (6.3) | 1.0 | | | 1.0 | | |
| Elevated, first tertile (100–111 mg/dl) | 218 | 19 (8.7) | 1.4 (0.8–2.5) | 0.26 | | 1.5 (0.8–2.6) | 0.21 | |
| Elevated, second tertile (112–129 mg/dl) | 219 | 39 (17.8) | 3.0 (1.9–4.9) | <0.0001 | | 3.0 (1.8–4.8) | <0.0001 | |
| Elevated, third tertile (≥130 mg/dl) | 222 | 84 (37.8) | 7.4 (4.8–11.3) | <0.0001 | | 5.3 (3.4–8.1) | <0.0001 | |
| Known diabetes | 462 | 108 (23.4) | 4.1 (2.7–6.3) | <0.0001 | | 2.8 (1.8–4.3) | <0.0001 | |

*All models are adjusted for the GRACE risk score. †To convert from milligrams per deciliter to millimoles per liter, multiply plasma glucose values by 0.0555. ‡The HR for the GRACE risk score was 1.36 per 10 points increase (95% CI 1.30–1.41, $P < 0.0001$). §The HR for the GRACE risk score was 1.38 per 10 points increase (1.30–1.46, $P < 0.0001$). ‖The HR for the GRACE risk score was 1.35 per 10 points increase (1.30–1.42, $P < 0.0001$). OR, odds ratio.

entire spectrum of patients with acute coronary syndromes (10).

The incremental additive information associated with the admission and fasting glucose variables over the GRACE risk score for the prediction of long-term mortality was assessed with the *c* statistics (22), using the methods described by DeLong et al. (23). Differences were considered statistically significant at the two-sided $P < 0.05$ level. Statistical analyses were performed using SPSS statistical software (version 12.0; SPSS, Chicago, IL) and MedCalc version 7.3.

**RESULTS** — A total of 1,101 nondiabetic and 462 diabetic patients were enrolled. The clinical characteristics of the patients according to categories of fasting glucose are shown in Table 1. Elevated fasting glucose was associated with older age, female sex, and higher BMI and triglycerides and a higher frequency of previous infarction, previous heart failure, and hypertension. Patients presenting with elevated fasting glucose had higher creatinine and higher heart rates and Killip class on admission and lower ejection fraction. They were less likely to receive coronary revascularization.

### Fasting glucose and long-term mortality

The median duration of follow-up was 24 months (range 6–48 months). During follow-up, 170 patients (15.4%) died. In a multivariable Cox model adjusting for the GRACE risk score, there was a highly significant interaction between history of diabetes and both admission glucose ($P = 0.002$) and fasting glucose levels ($P = 0.006$). Therefore, the relationship between glucose levels and long-term mortality was analyzed separately in patients with and without diabetes.

In nondiabetic patients, unadjusted analyses showed a stepwise increase in long-term mortality with increasing concentrations of both admission glucose (Table 2, model 1) and fasting glucose (Table 2, model 2, and Fig. 1). After adjustment for the GRACE risk score, both admission glucose and fasting glucose remained strong independent predictors of long-term mortality (Table 2, models 1 and 2). The *c* statistic of the prognostic model containing the GRACE risk score indicated satisfactory discrimination (*c* statistic 0.8 ± 0.02). The *c* statistic increased significantly when admission glucose (*c* statistic 0.83 ± 0.02; $P = 0.02$) and fasting glucose (*c* statistic 0.85 ± 0.02; $P = 0.004$) were added to the model that included the GRACE score.

To determine whether previously undiagnosed diabetes could account, in part, for the relationship between fasting glucose and outcome in nondiabetic patients, additional analyses were performed using combined data from patients with and without previously diagnosed diabetes. In these models, a fifth group of patients with known diabetes was added to four fasting glucose categories. Compared with patients with normal fasting glucose, the adjusted HR for long-term mortality in patients with previously known diabetes was 2.8 (95% CI 1.8–4.3;

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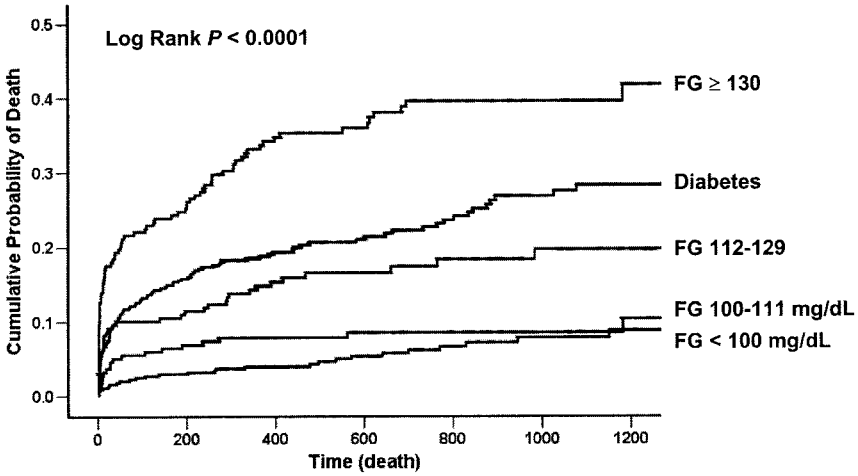


**Figure 1**—*Kaplan-Meier cumulative survival curves of patients with normal fasting glucose (FG), tertiles of elevated fasting glucose, and previously known diabetes (comparison by log-rank test).*

$P < 0.0001$). The HR for patients with known diabetes was similar to that of patients in the second elevated fasting glucose tertile and much lower than that of patients in the third elevated fasting glucose tertile (Table 2, model 3, and Fig. 1).

Within the group of patients with diabetes, there was no significant relationship between long-term mortality and AG. Compared with patients with normal AG, the adjusted HRs in patients with elevated AG were as follows: first tertile 0.9 (95% CI 0.5–1.6; $P = 0.84$); second tertile 1.2 (0.7–2.0; $P < 0.62$); third tertile 1.3 (0.8–2.1; $P < 0.32$) ($P_{trend} = 0.77$). Similar results were obtained for fasting glucose ($P_{trend} = 0.51$).

### Fasting glucose and left ventricular systolic function

The relationship between fasting glucose and LVEF was analyzed after 75 patients (4.8%) with missing data were excluded. Among patients without diabetes, there was a graded inverse relationship between LVEF and fasting glucose ($P < 0.0001$) (Fig. 2*A*). However, the inverse relationship between fasting glucose and LVEF was less apparent among patients with diabetes ($P = 0.06$) (Fig. 2*B*).

To investigate the interaction between fasting glucose and LVEF in relation to mortality, the nondiabetic patients were stratified into 16 groups according to the 4 categories of fasting glucose and 4 categories of LVEF. Figure 3 shows that for each level of LVEF mortality was lowest among subjects in the lowest fasting glucose category and highest in patients in the highest fasting glucose category. In a multivariate Cox mode with adjustments for the GRACE risk score and LVEF, fasting glucose remained a strong independent predictor of long-term mortality. The adjusted HR for mortality in tertiles of elevated fasting glucose compared with normal fasting glucose was as follows: first tertile 1.4 (95% CI 0.7–2.6; $P = 0.36$); second tertile 3.0 (1.7–5.1; $P < 0.0001$); and third tertile 4.2 (2.5–6.9; $P < 0.0001$).

**CONCLUSIONS** — In a prospective study of patients with AMI, we found a graded independent association between glucose levels at admission and long-term mortality in nondiabetic patients. Both admission and fasting glucose levels provided incremental prognostic informa-

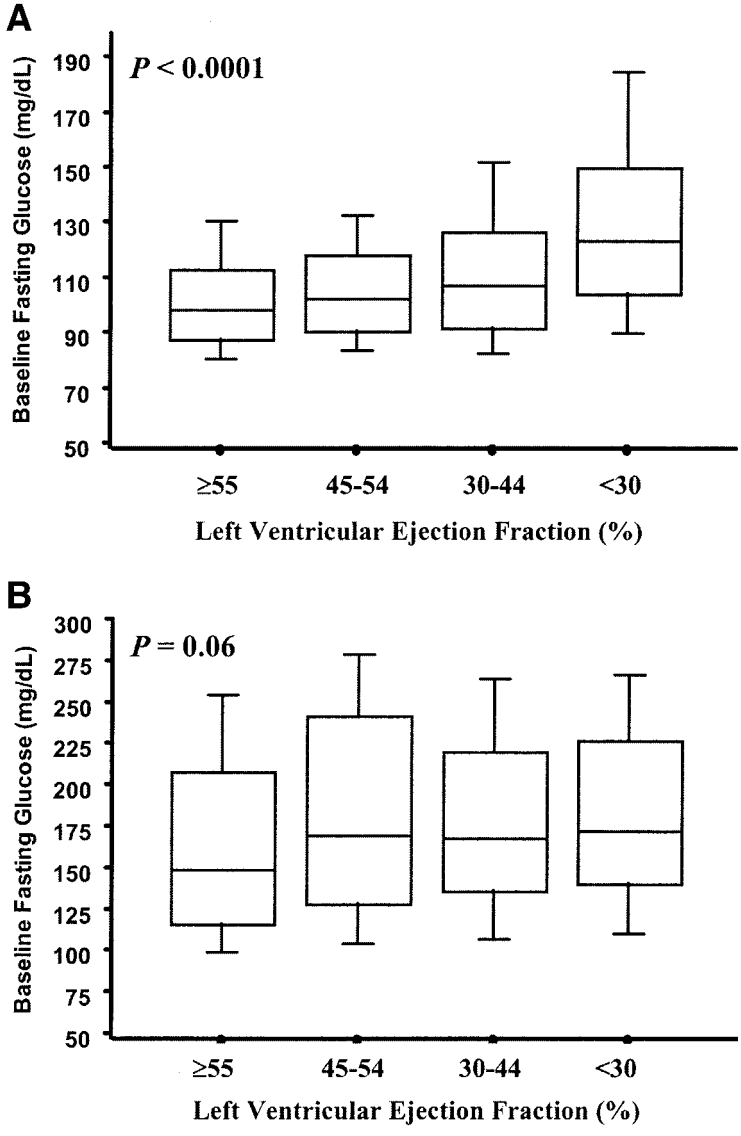


**Figure 2**—*Box-and-whisker plots of fasting glucose levels according to the LVEF in patients without* (A) *and with* (B) *previously known diabetes. The line within the box denotes the median and the box spans the interquartile range (25th–75th percentiles). Whiskers extend from the 10th–90th percentiles.*

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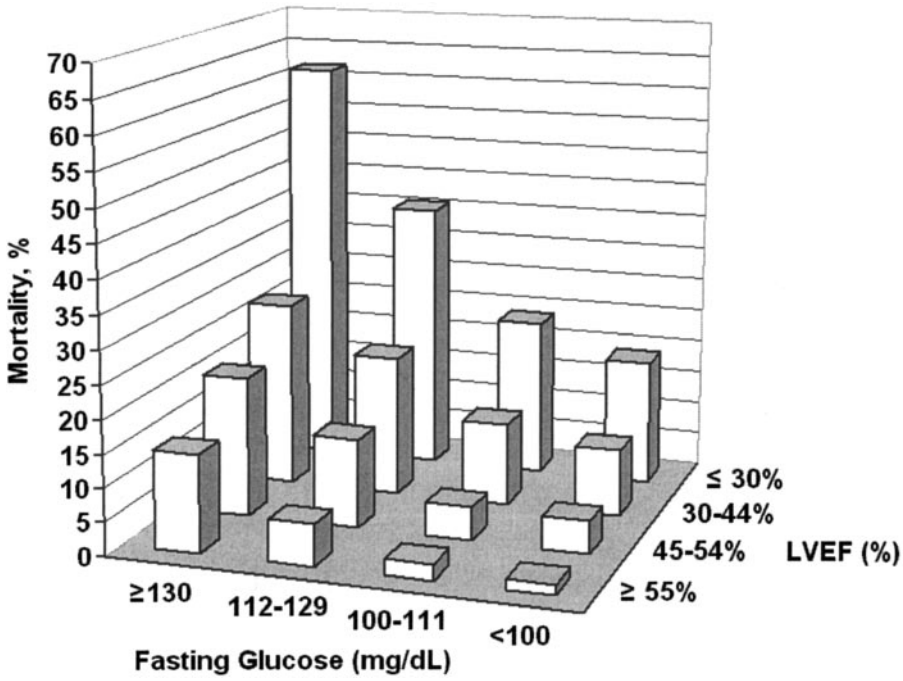


**Figure 3—***Mortality according to fasting glucose categories and LVEF.*

tion with regard to long-term mortality when added to the GRACE risk score. However, fasting glucose provided greater incremental prognostic information than admission glucose. Furthermore, fasting glucose remained an independent predictor of long-term mortality after adjustment for LVEF.

### Fasting glucose as a predictor of mortality in AMI

We have previously shown that fasting glucose is better than admission glucose for the prediction of 30-day mortality in nondiabetic patients with AMI (7). In the present study, we demonstrate that fasting glucose remains a superior predictor of long-term mortality. Furthermore, fasting glucose is a simple robust marker for predicting long-term mortality in nondiabetic patients that provides incremental prognostic information when added to the GRACE risk score. Previously undiagnosed diabetes cannot account for the increased mortality associated with elevated fasting glucose in nondiabetic patients because the risk associated with prior diagnosis of diabetes was considerably lower compared with that of nondiabetic patients with fasting glucose in the upper tertile.

### Fasting glucose and left ventricular function

In many patients with AMI, the acute injury to the myocardium leads to transient or permanent heart failure. Patients with heart failure exhibit insulin resistance, characterized by both fasting and stimulated hyperinsulinemia (12). Consequently, glucose intolerance is extremely common in patients with heart failure (13), and patients with heart failure are at an increased risk of developing type 2 diabetes (24).

Thus, stress hyperglycemia may be a marker of severe cardiac damage, leading to overt or subclinical heart failure. However, the relation between glucose concentrations and infarct size is controversial. O'Sullivan et al. (15) and Thomassen et al. (16) found no correlation between glucose levels and infarct size as reflected in peak levels of cardiac enzymes, whereas Oswald et al. (17) and Bellodi et al. (18) found a weak relation between plasma glucose concentrations and infarct size. Recently, Ishihara et al. (15) found lower LVEF among patients with AMI and admission glucose >10 mmol/l (14). These investigators suggested that impaired LVEF might explain the poor outcomes of patients with AMI and elevated admission glucose (14).

In the present study, we observed a graded increase in mortality with increasing fasting glucose concentrations at each level of LVEF, including patients with preserved LVEF. Importantly, baseline fasting glucose remained a powerful predictor of mortality even after adjustments for the GRACE risk score and LVEF. These results indicate that although impaired LVEF contributes to stress hyperglycemia, the strong association between fasting glucose and mortality is not merely a reflection of a severely damaged myocardium.

### Fasting glucose in patients with diabetes

We have previously reported that the relationship between increasing levels of admission glucose and fasting glucose and 30-day mortality was much weaker among patients with diabetes (7). Recent large studies have also shown that the association between admission glucose and mortality is less pronounced or absent in patients with diabetes (3,5). In the present study, there was no significant relationship between long-term mortality and either admission glucose or fasting glucose levels among patients with diabetes. Similarly, the inverse relationship between fasting glucose and LVEF was markedly attenuated in patients with diabetes. These results indicate that the underlying metabolic abnormalities in insulin secretion and action in the presence of diabetes and the quality of glycemic control become the dominant determinants of plasma glucose levels in the setting of AMI. Thus, hyperglycemia due to uncontrolled diabetes may mask stress-induced changes in glucose metabolism.

### Mechanism of stress hyperglycemia

Potential mechanisms for the association between hyperglycemia in the acute phase of AMI and mortality have been reviewed previously. These include induction of endothelial dysfunction, oxidative stress, inflammation, hypercoagulability, and impaired fibrinolysis (25).

Elevation of fasting glucose levels in AMI may incorporate the cumulative effects of activation of multiple neurohormonal pathways such as catecholamines, cortisol, and growth hormone (17,26), which can produce or augment insulin resistance (27–29). Activation of the renin-angiotensin system (30) and the effect of increased circulating cytokines (31) such as tumor necrosis factor-α in the setting of AMI infarction may also contribute to a reduction in peripheral insulin sensitivity (32,33). Exaggerated neurohormonal and cytokine activation may lead to hyperglycemia and, in parallel, induces myocardial damage and adverse remodeling (34,35).

Elevated fasting glucose is also a marker of relative insulin deficiency that reduces glucose uptake by the ischemic

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myocardium and promote lipolysis and increased circulating free fatty acids. These metabolic alterations may impair the energetic and functional adaptation of the heart to ischemia or hemodynamic overload (36,37). In addition, insulin has putative direct cell survival effects during AMI and other critical illness (38). Insulin has been reported to attenuate cardiomyocyte apoptosis (39), promote ischemic preconditioning, lessen ischemia-reperfusion injury, and exhibit anti-inflammatory actions (38,40).

### Study limitations

Our study has several important limitations. The study was prospective in patient enrollment but observational in nature. Information on the extent of neurohormonal activation was not available in the study patients. In addition, there was no information on other possible mediators that may contribute to the adverse outcome of patients with elevated fasting glucose such as free fatty acid.

In summary, fasting glucose is a simple robust tool for predicting long-term mortality in nondiabetic patients with AMI. Fasting glucose provides incremental prognostic information when added to the GRACE risk score. The relationship between elevated fasting glucose and long-term mortality is independent of LVEF. Fasting glucose is not a useful prognostic marker in patients with diabetes.


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