Effect of Abnormal Fasting Plasma Glucose Level on All-Cause Mortality in Older Patients With Acute Myocardial Infarction: Results From the Beijing Elderly Acute Myocardial Infarction Study (BEAMIS)

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OBJECTIVE: To assess whether the relationship between abnormal fasting plasma glucose (FPG) levels and patient outcomes holds for both older men and older women with acute myocardial infarction (AMI).

PATIENTS AND METHODS: From April 1, 2004, to October 31, 2006, a total of 2016 consecutive older patients (age ≥ 65 years) presenting with AMI were screened. Of these patients, 1854 were consecutively enrolled in the study. Patients were categorized into 4 groups: the hypoglycemic group (FPG, ≤ 90.0 mg/dL [to convert to mmol/L, multiply by 0.0555]; $n=443$, 23.9%), the euglycemic group (FPG, 90.1-126.0 mg/dL; $n=812$, 43.8%), the mildly hyperglycemic group (FPG, 126.1-162.0 mg/dL; $n=308$, 16.6%), and the severely hyperglycemic group (FPG, ≥ 162.1 mg/dL; $n=291$, 15.7%). The primary outcomes were rates of in-hospital and 3-year mortality.

RESULTS: Female patients were older and had a higher incidence of diabetes mellitus but lower rates of smoking and use of invasive therapy. Men tended to have a higher frequency of hypoglycemia, whereas women tended to have a higher frequency of hyperglycemia. No significant difference was found in in-hospital (10.9% vs 9.1%; $P=.36$) or 3-year (24.5% vs 24.5%; $P=.99$) mortality between male and female patients, and FPG-associated mortality did not vary significantly by sex.

CONCLUSION: An increased FPG level was associated with a relatively higher risk of in-hospital mortality in men but not in women. Nonetheless, increased and decreased FPG levels at admission could predict higher mortality rates regardless of sex. There was a striking U-shaped relationship between FPG levels and in-hospital and 3-year mortality. The effect of abnormal FPG level on outcomes among older patients with AMI did not vary significantly by sex.

Mayo Clin Proc. 2011;86(2):94-104

AMI = acute myocardial infarction; BEAMIS = the Beijing Elderly Acute Myocardial Infarction Study; CABG = coronary artery bypass grafting; CI = confidence interval; DM = diabetes mellitus; FPG = fasting plasma glucose; PCI = percutaneous coronary intervention

Many primary and secondary prevention strategies for acute myocardial infarction (AMI) shown to be efficacious in randomized controlled trials have been implemented by physicians and health care systems, resulting in improved control of cardiovascular risk factors in several populations.¹⁻⁵ Although better management of risk factors is an important quality benchmark, reductions in the incidence of myocardial infarction and mortality are

better measures of quality. Previous studies of mortality associated with AMI have often focused on selected subgroups in populations with limited diversity with respect to coexisting conditions, and most have not examined differences due to sex, although management and outcomes differ markedly.⁶⁻⁹ Several studies have reported that acute hyperglycemia in patients with AMI is related to a higher incidence of mortality.¹⁰⁻¹⁶ No studies have evaluated the relationship between abnormal fasting plasma glucose (FPG) levels and outcomes separately for men and women. The aim of this study, therefore, was to assess whether the relationship between FPG levels and all-cause mortality is different for men and women among older patients with AMI by analyzing data from BEAMIS (the Beijing Elderly Acute Myocardial Infarction Study).

PATIENTS AND METHODS

BEAMIS is an observational study conducted at 5 medical centers. Detailed clinical data were abstracted from medical records by trained medical record reviewers. From April 1, 2004, to October 31, 2006, a total of 2016 consecutive older (age ≥ 65 years) patients presenting with AMI were screened. All patients underwent coronary angiogra-

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BEAMIS was supported by grant Z0005190042811 from the Beijing Municipal Science & Technology Commission. The sponsor had no involvement in the collection, analysis, or interpretation of data; in the writing of the submitted manuscript; or in the decision to submit the manuscript for publication.

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phy. Patients with unstable angina pectoris (myocardial biomarker levels ≤ 2 times the corresponding normal upper limits) were excluded. To enhance homogeneity and ensure examination of a representative cohort in the context of contemporary treatment modalities, 22 patients (1.1%) who underwent percutaneous transluminal coronary angioplasty without stent implantation and 135 patients (6.7%) who underwent bare-metal stent implantation were excluded. Five patients (0.2%) with a terminal illness were also excluded. After exclusions, the study group comprised 1854 patients, and FPG levels were measured in all study patients. Blood samples for FPG level determination were obtained after an overnight fast of at least 8 hours, within 24 hours of admission. Plasma glucose levels were enzymatically determined with the glucose oxidase method.¹⁷ Of the study patients, 39.5% were receiving conservative medical therapy; 47.5%, percutaneous coronary intervention (PCI); and 13.0%, coronary artery bypass grafting (CABG). For patients receiving PCI or CABG, medications (such as aspirin, clopidogrel, β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, antidiabetic agents, statins, and others) were also given according to American College of Cardiology/American Heart Association guidelines. A total of 104 patients (5.7%) were treated with thrombolysis, most (83/104) with urokinase. The study protocol was reviewed and approved by the ethics committee of each participating institution.

STUDY DEFINITIONS

We defined AMI by a combination of 2 of the 3 following characteristics: chest pain consistent with ongoing myocardial ischemia persisting for more than 30 minutes, ischemic electrocardiographic changes, and peak levels of myocardial biomarkers (including creatine kinase MB and troponin I, cardiac form/troponin T, cardiac form) more than 2 times the corresponding normal upper limits.¹⁸ Patients were classified as having recognized diabetes mellitus (DM) if their medical records contained documentation of a history of DM, they were diagnosed as having DM on admission, or they were taking an antidiabetic agent at the time of admission. Killip classification was assigned as follows: individuals with no clinical signs of heart failure were assigned to Killip class I; those with rales or crackles in the lungs, an S_3 gallop, and elevated jugular pressure, to Killip class II; (3) those with frank acute pulmonary edema, to Killip class III; and (4) those in cardiogenic shock or with hypotension (measured as systolic blood pressure lower than 90 mm Hg) and evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating), to Killip class IV.¹⁹

OUTCOMES

The primary outcomes were rates of in-hospital and 3-year mortality. Glucose metabolism disturbance in patients with AMI has been thought to be induced by stress.¹⁰⁻¹⁴ Whether this glucose metabolism disturbance has an impact on outcomes in the acute phase only is not known. Accordingly, we evaluated the relationship between abnormal FPG levels and in-hospital and 3-year mortality separately.

STATISTICAL ANALYSES

All case record form data were entered into 2 EpiData 3.1 databases (Epidata Association, Odense, Denmark) by different people. Analyses were conducted with the SPSS 16.0 software package (SPSS Inc, Chicago, IL). Baseline demographic and clinical characteristics were compared with the Pearson χ^2 test for categorical variables and the nonrepeated analysis of variance test for continuous variables. The unadjusted relationship between groups of admission FPG level and in-hospital and 3-year mortality was tested with the Pearson χ^2 test. Cox proportional models were used to assess whether the relationship between admission FPG level and in-hospital and 3-year mortality was independent of other characteristics. Variables clinically considered or previously demonstrated to be of prognostic importance and those identified in bivariate analyses as predictors of in-hospital and 3-year mortality were entered into the models.²⁰

RESULTS

BASILINE CHARACTERISTICS AND MEDICATION USE

A total of 1161 men (62.6%) and 693 women (37.4%) diagnosed as having AMI were included in the data analysis. Demographic and clinical characteristics are given in Table 1. The mean $\pm$ SD patient age was 72.5 ± 5.5 years (72.1 ± 5.2 years for men vs 73.2 ± 5.8 for women, $P = .02$). Only 24.6% of the patients (19.5% of men vs 33.2% of women; $P < .001$) had a history of recognized DM. Current smoking was documented in 29.1% of patients (40.3% of men vs 10.2% of women; $P < .001$). The prevalence of prior myocardial infarction and stroke was 10.6% and 14.1%, respectively; no significant differences were noted between men and women. Left ventricular ejection fraction and distribution of Killip class among men and women were similar. Approximately 46.6% of the patients were Killip class I, with the rest meeting criteria for Killip class II to IV. Levels of myocardial biomarkers and creatinine did not vary significantly by sex. Men and women were given the same medications during admission; however, fewer female patients underwent invasive revascularization therapy (including PCI and CABG).

TABLE 1. Demographic and Clinical Characteristics of the Study Participants^{a,b,c}

Characteristic	Overall (N=1854)	Stratified by sex		P value
		Male (n=1161)	Female (n=693)	
Age (y)	72.5±5.5	72.1±5.2	73.2±5.8	.02
DM	456 (24.6)	226 (19.5)	230 (33.2)	<.001
Prior MI	196 (10.6)	125 (10.8)	71 (10.2)	.74
Prior stroke	261 (14.1)	166 (14.3)	95 (13.7)	.81
Current smoking	539 (29.1)	468 (40.3)	71 (10.2)	<.001
Killip class				.80
I	864 (46.6)	548 (47.2)	316 (45.6)	
II	489 (26.4)	309 (26.6)	180 (26.0)	
III	334 (18.0)	203 (17.5)	131 (18.9)	
IV	167 (9.0)	94 (8.1)	73 (10.5)	
BMI (kg/m ²)	25.4±3.1	25.3±2.7	25.5±4.1	.89
Initial laboratory test results				
CK-MB (U/L)	248.2±42.7	243.8±39.6	251.5±49.3	.77
TnI (ng/mL)	46.2±20.9	44.1±17.9	48.3±24.0	.57
Creatinine (mg/dL)	1.1±0.67	1.2±0.7	1.0±0.7	.02
FPG (mg/dL)	126.1±57.7	122.5±55.9	131.5±59.5	.04
LDL-C (mg/dL)	104±35	100±35	112±35	<.001
LVEF (%)	52.8±11.5	52.9±11.7	52.7±11.3	.91
Diagnosis				.70
STEMI	1476 (79.6)	930 (80.1)	546 (78.8)	
NSTEMI	378 (20.4)	231 (19.9)	147 (21.2)	
Treatments				<.001
Medication	732 (39.5)	382 (32.9)	350 (50.5)	
PCI	881 (47.5)	608 (52.4)	273 (39.4)	
CABG	241 (13.0)	170 (14.6)	71 (10.2)	
Medications in hospital				
Aspirin	1793 (96.7)	1112 (95.8)	681 (98.3)	.16
Clopidogrel	1517 (81.8)	954 (82.2)	563 (81.2)	.66
LMWH	1632 (88.0)	1005 (86.6)	627 (90.5)	.25
β-Blocker	1695 (91.4)	1032 (88.9)	663 (95.7)	.007
CCB	348 (18.8)	205 (17.7)	143 (20.6)	.43
ACEI	1425 (76.9)	871 (75.0)	554 (79.9)	.22
ARB	284 (15.3)	181 (15.6)	103 (14.9)	.80
Nitrate	1600 (86.3)	1000 (86.1)	600 (86.6)	.72
Anti-DM	466 (25.1)	269 (23.2)	197 (28.4)	.15
Insulin	44 (2.4)	24 (2.1)	20 (2.9)	.13
Statin	1777 (95.8)	1104 (95.1)	673 (97.1)	.32
Thrombolytics	104 (5.6)	66 (5.7)	38 (5.5)	.42
Mortality				
In-hospital	190 (10.3)	127 (10.9)	63 (9.1)	.36
3-y	455 (24.5)	285 (24.5)	170 (24.5)	.99

^a ACEI = angiotensin-converting enzyme inhibitor; Anti-DM = antidiabetic agent; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CK-MB = creatine kinase MB; DM = diabetes mellitus; FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; LMWH = low-molecular-weight heparin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TnI = troponin I, cardiac form.

^b Categorical data are provided as number (percentage) of patients and continuous data as mean ± SD.

^c SI conversion factors: To convert CK-MB values to μg/L, multiply by 1; to convert creatinine values to μmol/L, multiply by 88.4; to convert FPG values to mmol/L, multiply by 0.0555; to convert LDL-C values to mmol/L, multiply by 0.0259; to convert TnI values to μg/L, multiply by 1.

DISTRIBUTION OF ADMISSION FPG LEVELS

The median admission FPG level was 108.1 mg/dL (range, 45.0-482.9 mg/dL [to convert to mmol/L, multiply by 0.0555]), with a mean ± SD value of 126.1±57.7 mg/dL (122.±55.9 mg/dL in men vs 131.5±59.5 mg/dL in women;

P=.04). Distribution of admission FPG levels in male and female patients is shown in Figure 1, A. Most patients (84.3%) had admission FPG values between 73.9 and 180.2 mg/dL (73.9 mg/dL ≤ FPG ≤ 108.1 mg/dL, 47.5%; 109.9 mg/dL ≤ FPG ≤ 144.1 mg/dL, 26.7%; 146.0 mg/dL

$\leq$ FPG $\leq$ 180.2 mg/dL, 9.2%). According to admission FPG level and clinical indication, patients were categorized into 4 groups: the hypoglycemic group (FPG, $\leq$ 90.0 mg/dL; n=443, 23.9%), the euglycemic group (FPG, 90.1-126.0 mg/dL; n=812, 43.8%), the mildly hyperglycemic group (FPG, 126.1-162.0 mg/dL; n=308, 16.6%), and the severely hyperglycemic group (FPG $\geq$ 162.1 mg/dL; n=291, 15.7%). Male patients tended to have a higher frequency of hypoglycemia, whereas female patients tended to have a higher frequency of hyperglycemia (Figure 1, B; $P=.006$). However, central tendency and dispersion were similar between men and women (Figure 1, C).

SEX-STRATIFIED COMPARISON OF THE CHARACTERISTICS AMONG DIFFERENT FPG GROUPS

The demographic and clinical characteristics of the 4 FPG groups did not vary significantly by sex, except for the prevalence of recognized DM, Killip class, and frequency of use of antidiabetic agents (Table 2). Groups with higher FPG admission levels were more likely to have a history of recognized DM and a higher Killip class and to be using antidiabetic agents (including insulin) than groups with lower admission FPG levels.

FPG-STRATIFIED COMPARISON OF CHARACTERISTICS BETWEEN MALE AND FEMALE PATIENTS

An FPG-stratified comparison between male and female patients was undertaken to further examine whether important characteristics vary by sex. As indicated in Table 3, only the prevalence of recognized DM in patients with hypoglycemia differed by sex (7.9% in men vs 20.5% in women; $P=.04$). No significant differences between men and women were found in any of the other characteristics at any FPG level.

DIFFERENCES BETWEEN MEN AND WOMEN IN THE EFFECT OF FPG LEVEL ON ALL-CAUSE MORTALITY

In the overall cohort, 190 patients (10.2%) died in the hospital and 455 patients (24.5%) died during the 3-year follow-up period (Table 1). Furthermore, differences in in-hospital and 3-year mortality did not differ significantly by sex (in-hospital mortality: 10.9% for men vs 9.1% for women; $P=.36$; 3-year mortality: 24.5% for men vs 24.5% for women; $P=.99$). Sex-stratified analysis of the mortality among different FPG groups was performed (Table 2). In the overall cohort, both the hypoglycemic and hyperglycemic groups were associated with higher in-hospital and 3-year all-cause mortality rates compared with the euglycemic group (in-hospital mortality: FPG, $\leq$ 90.0 mg/dL, 10.0%; FPG, 90.1-126.0 mg/dL, 6.6%; FPG, 126.1-162.0 mg/dL, 11.3%; and FPG, $\geq$ 162.1 mg/dL, 19.6%; 3-year mortality: FPG, $\leq$ 90.0 mg/dL, 23.7%; FPG, 90.1-126.0 mg/dL, 15.8%; FPG, 126.1-162.0 mg/dL,

FIGURE 1. Distribution of admission fasting plasma glucose (FPG) levels. A, Distribution of admission FPG levels in male and female patients. B, Distribution of hypoglycemia and hyperglycemia in male and female patients. C, Sex-based differences in the central tendency and dispersion of FPG levels in the hypoglycemic and hyperglycemic groups. To convert FPG levels to mmol/L, multiply by 0.0555. F = female; M = male.

TABLE 2. Sex-Stratified Comparison of the Demographic and Clinical Characteristics of Different FPG Groups^{a,b,c}

Characteristic	Male (n=1161)					Female (n=693)				
	Hypo-glycemic (n=320)	Eugly-cemic (n=517)	Mildly glycemic (n=156)	Severely hyper-glycemic (n=168)	P value	Hypo-glycemic (n=123)	Eugly-cemic (n=295)	Mildly hyper-glycemic (n=152)	Severely hyper-glycemic (n=123)	P value
Age (y)	72.8±5.5	72.0±5.3	72.1±4.9	71.2±4.9	.34	73.3±5.2	73.5±6.2	72.5±5.1	73.2±6.2	.80
DM	7.9	11.8	32.7	52.8	<.001	20.5	16.0	45.8	71.8	<.001
Prior MI	8.2	10.4	19.1	10.2	.27	13.2	9.2	6.5	13.2	.65
Prior stroke	15.9	16.4	10.4	7.5	.35	13.1	11.6	16.6	17.8	.77
Current smoking	42.8	40.7	35.1	33.5	.74	13.2	12.8	8.5	6.4	.72
Killip class					.03					.40
I	59.2	48.1	30.6	37.3		64.1	41.8	45.8	35.9	
II	24.3	28.1	32.7	23.4		18.1	27.3	23.1	30.9	
III	10.3	16.1	26.5	25.6		7.6	20.3	20.7	25.6	
IV	6.0	7.3	10.2	13.7		10.4	11.0	10.5	7.8	
BMI (kg/m ²)	25.9±2.7	24.8±2.4	26.5±3.4	25.1±2.5	.44	23.4±5.1	26.4±3.3	28.8±2.5	21.8±2.0	.12
Initial laboratory test results										
CK-MB (U/L)	247.1±51.6	241.0±33.8	250.3±40.5	245.6±57.8	.63	244.8±60.9	257.2±61.3	255.7±51.1	259.4±62.6	.44
TnI (ng/mL)	46.0±20.3	42.7±25.8	47.4±25.7	44.3±18.9	.23	44.1±29.9	48.0±22.5	47.8±35.3	51.2±31.4	.32
Creatinine (mg/dL)	1.2±0.8	1.1±0.6	1.1±0.4	1.3±0.8	.61	1.2±0.6	1.0±0.6	0.9±0.3	1.0±0.4	.25
FPG (mg/dL)	81.1±7.2	106.3±10.8	142.3±9.0	232.4±70.3	<.001	79.3±10.8	106.3±10.8	142.3±10.8	236.0±59.5	<.001
LDL-C (mg/dL)	97±39	97±27	100±31	108±39	.12	116±35	108±35	112±39	124±39	.20
LVEF (%)	54.7±11.4	53.5±11.2	50.1±11.2	50.3±12.9	.08	50.4±11.7	51.8±12.1	53.8±11.2	55.2±9.3	.29
Diagnosis										.70
STEMI	79.3	82.9	71.4	79.3	.38	74.4	77.3	83.2	82.1	
NSTEMI	20.7	17.1	28.6	20.7	.38	25.6	22.7	16.8	17.9	
Treatments					.53					.77
Medication	29.6	32.4	28.6	45.3		48.8	50.6	43.9	59.0	
PCI	55.5	53.5	55.1	39.6		38.4	41.8	43.7	30.8	
CABG	14.8	14.0	16.3	15.1		12.8	7.6	12.6	10.3	
In-hospital medications										
Aspirin	97.0	96.2	93.9	94.3	.75	97.4	99.0	97.9	97.4	.91
Clopidogrel	86.8	84.9	71.4	77.3	.07	74.6	84.2	79.4	79.6	.64
LMWH	88.8	86.1	89.8	82.9	.69	84.8	92.9	89.8	87.4	.55
β-Blocker	85.1	91.4	89.8	86.8	.44	97.4	97.7	93.7	92.3	.40
CCB	16.1	16.9	22.4	17.4	.79	20.5	23.5	14.5	23.0	.64
ACEI	67.1	79.2	73.6	75.6	.19	79.5	81.5	74.9	84.5	.69
ARB	12.1	16.3	16.3	17.1	.78	12.6	17.1	18.6	10.2	.65
Nitrate	90.5	84.1	83.9	77.7	.21	92.2	91.0	85.3	73.6	.06
Anti-DM	12.2	18.9	32.7	45.4	<.001	23.0	19.1	37.3	48.5	.003
Insulin	1.6	1.9	2.6	3.0	.03	1.6	2.0	3.9	4.9	.02
Statin	92.5	97.1	88.0	92.7	.16	94.9	99.0	91.9	100.0	.07
Thrombolytics	5.0	5.8	5.1	7.1	.15	5.7	4.7	5.9	6.5	.37
Mortality										
In-hospital	9.9	6.7	12.2	24.5	.004	10.3	6.5	10.4	12.8	.04
3-y	24.2	15.1	32.7	46.3	<.001	21.8	17.2	27.5	41.1	.02

^a ACEI = angiotensin-converting enzyme inhibitor; Anti-DM = antidiabetic agent; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CK-MB = creatine kinase MB; DM = diabetes mellitus; FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; LMWH = low-molecular-weight heparin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TnI = troponin I, cardiac form.

^b Categorical data are provided as percentage of patients and continuous data as mean ± SD.

^c SI conversion factors: To convert CK-MB values to µg/L, multiply by 1; to convert creatinine values to µmol/L, multiply by 88.4; to convert FPG values to mmol/L, multiply by 0.0555; to convert LDL-C values to mmol/L, multiply by 0.0259; to convert TnI values to µg/L, multiply by 1.

30.5%; and FPG, ≥162.1 mg/dL, 44.0%). Patients in the group with an FPG of 90.1 to 126.0 mg/dL had the best outcome, and there was a striking U-shaped relationship between admission FPG levels and in-hospital and 3-year all-cause mortality (Figure 2, A). Moreover, a U-shaped relationship persisted between admission FPG levels and mortality regardless of sex (Figure 2, B and C).

Table 2 summarizes the in-hospital and 3-year mortality rates for each of the FPG groups, stratified by sex. An increased FPG level was associated with a relatively higher risk of in-hospital mortality in men but not in women. However, hypoglycemia or hyperglycemia predicted higher in-hospital and 3-year all-cause mortality rates in both men and women. The rate of FPG-

TABLE 3. **FPG-Stratified Comparison of the Characteristics of Male and Female Patients^{a,b,c}**

Characteristic	Male	Female	P value
Hypoglycemic (n=443)			
FPG (mg/dL)	81.1±7.2	79.3±10.8	.59
DM	7.9	20.5	.04
Anti-DM	12.2	23.0	.10
Insulin	1.6	1.6	>.99
In-hospital mortality	9.9	10.3	.95
3-y mortality	24.2	21.8	.74
Euglycemic (n=812)			
FPG (mg/dL)	106.3±10.8	106.3±10.8	.98
DM	11.8	16.0	.31
Anti-DM	18.9	19.1	.89
Insulin	1.9	2.0	.96
In-hospital mortality	6.7	6.5	.93
3-y mortality	15.1	17.2	.63
Mildly hyperglycemic (n=308)			
FPG (mg/dL)	142.3±9.0	142.3±10.8	.96
DM	32.7	45.8	.18
Anti-DM	32.7	37.3	.62
Insulin	2.6	3.9	.51
In-hospital mortality	12.2	10.4	.78
3-y mortality	32.7	27.5	.56
Severely hyperglycemic (n=291)			
FPG (mg/dL)	232.4±70.3	236.0±59.5	.75
DM	52.8	71.8	.07
Anti-DM	45.4	48.5	.74
Insulin	3.0	4.9	.25
In-hospital mortality	24.5	12.8	.06
3-y mortality	46.3	41.1	.60

^a Anti-DM = antidiabetic agent; DM = diabetes mellitus; FPG = fasting plasma glucose.

^b Categorical data are provided as percentage of patients and continuous data as mean ± SD.

^c SI conversion factor: To convert FPG values to mmol/L, multiply by 0.0555.

associated mortality did not differ significantly by sex (Table 3).

After multivariate adjustment, patients with hyperglycemia or hypoglycemia tended to have increased risks for both in-hospital (Figure 3, A) and 3-year (Figure 3, B) mortality compared with the euglycemic population. The FPG-stratified hazard ratios and 95% confidence intervals (CIs) for in-hospital mortality in male vs female patients were as follows: 90.0 mg/dL or less, 1.424 (95% CI, 1.255-2.934) vs 1.958 (95% CI, 1.219-3.008); 126.1 to 162.0 mg/dL, 2.106 (95% CI, 1.626-4.034) vs 1.037 (95% CI, 0.820-2.262); and 162.1 mg/dL or higher, 4.580 (95% CI, 2.188-7.356) vs 1.174 (95% CI, 0.905-4.432). The FPG-stratified hazard ratios for 3-year mortality in male vs female patients were as follows: 90.0 mg/dL or less, 1.603 (95% CI, 1.084-3.571) vs 1.157 (95% CI, 1.018-3.240); 126.1 to 162.0 mg/dL, 2.143 (95% CI, 1.407-5.282) vs 1.374 (95% CI, 1.159-3.691); and 162.1 mg/dL or higher, 2.775 (95% CI, 1.463-6.289) vs 1.958 (95% CI, 1.433-5.706). Hypoglycemia was associated with a significant increase in relative risk of in-hospital and 3-year mortality in the

FIGURE 2. Relationship between admission fasting plasma glucose (FPG) levels and mortality. A, Relationship between admission FPG levels and in-hospital and 3-year mortality in all patients. B, Relationship between admission FPG levels and in-hospital mortality, stratified by sex. C, Relationship between admission FPG levels and 3-year mortality rates, stratified by sex.

FIGURE 3. After multivariate adjustment, patients with hyperglycemia or hypoglycemia tended to have increased risks of both in-hospital and 3-year mortality compared with the euglycemic population. Hazard ratios (HRs) are provided for in-hospital mortality (A) and 3-year mortality (B). CI = confidence interval.

overall patient population. It is noteworthy that there was no significant difference in the effect of hyperglycemia on short-term mortality in women. The FPG-associated probability of survival in male and female patients is shown using in-hospital (Figure 4) and 3-year (Figure 5) Kaplan-Meier curves.

DISCUSSION

CLINICAL CHARACTERISTICS, MANAGEMENT, AND OUTCOMES IN MALE VS FEMALE PATIENTS WITH AMI

Recent measures to reduce risk factors at both the individual and population levels, including public bans on smoking and lower target levels of low-density lipoprotein cholesterol and blood pressure, have resulted in improved control of risk factors over time.¹⁻⁵ Each of these improvements in medical care might be expected to reduce the mortality associated with AMI. Although the overall adjusted mortality rate has decreased over time, mortality rates in men and women have remained dissimilar.⁶⁻⁹ Data from the prethrombolytic era showed that the mortality rates in male and female patients with AMI were 16% and 28%, respectively.⁶ Results from the

National Registry of Myocardial Infarction I, which enrolled more than 350,000 patients with AMI, showed that women had nearly twice the mortality rates of men, even after adjusting for age and risk factors.⁷ A retrospective cohort study by Vakili et al,⁸ including all patients with AMI who were treated by primary angioplasty in New York State in 1995, found that women had 2.3-fold higher risk of in-hospital mortality compared with men, despite similar angiographic settings. Gottlieb et al⁹ prospectively enrolled AMI patients in the 1990s in a community-based population and reported that women with AMI felt significantly worse than men at 30 days but not thereafter at 1 year. The reason for women being at a disadvantage when admitted for AMI was hotly discussed. Our study highlights several differences in the presenting clinical characteristics and management of male vs female patients with AMI that are consistent with those in other trials.^{7,21} Female patients with AMI presented at an older age and with a higher incidence of DM but with lower rates of smoking and use of invasive therapy (either PCI or CABG) than male patients.

With the advances in revascularization techniques and the availability of many primary or secondary prevention

FIGURE 4. In-hospital Kaplan-Meier survival curves according to fasting plasma glucose levels for male patients (A) and female patients (B).

medications in the past decade, the sex disparity in patients with AMI has vanished in recent reports.^{22,23} A propensity score–matched analysis of 3329 women and 3329 men with AMI showed the difference in mortality was not statistically significant (1.59% vs 1.92%; $P=.39$).²² The Tokai Acute Myocardial Infarction Study II prospectively included 2614 patients with AMI (566 women and

2048 men) admitted to the study hospitals in Japan from 2001 to 2003, and the results showed no significant difference in in-hospital mortality between male and female patients.²³ These findings are consistent with those of the current study (in-hospital mortality rate: 10.9% for men vs 9.1% for women; $P=.36$; 3-year mortality: 24.5% for men vs 24.5% for women; $P=.99$).

FIGURE 5. Three-year Kaplan-Meier survival curves according to fasting plasma glucose levels for male patients (A) and female patients (B).

RELATIONSHIP BETWEEN ABNORMAL PLASMA GLUCOSE LEVELS AND MORTALITY

Several studies have reported that acute hyperglycemia is related to a higher incidence of mortality.¹⁰⁻¹⁶ Most of the older and smaller studies (predominantly from the 1980s and 1990s) were summarized in the meta-analysis by Capes et al.¹⁰ These combined results demonstrated that the relative risk of in-hospital mortality in nondiabetic AMI patients with an admission FPG level less than 109.9 mg/dL was 3.9, compared with nondiabetic AMI patients who were euglycemic.¹⁰ Among AMI patients with DM, those with an admission glucose level higher than 180.2 mg/dL had a 70% increase in the relative risk of in-hospital mortality, compared with diabetic patients with normal admission glucose levels.¹⁰ More recent studies have confirmed these findings, showing significant increases in the risk of short- and long-term mortality, as well as heart failure, in hyperglycemic AMI patients both with and without known DM.^{11,12} These findings extend to the entire range of acute coronary syndromes, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina.¹³

Several studies also have documented a clear relationship between an elevated FPG level during AMI hospitalization and increased mortality risk.^{24,25} In contrast to a random glucose level on admission, an elevated FPG level may better reflect abnormalities in underlying glucose metabolism and thus may be a better predictor of outcomes. In one of the earlier studies on this issue, Suleiman et al²⁴ demonstrated that, although both admission glucose and FPG levels predicted 30-day mortality in nondiabetic patients with AMI, FPG level was the better discriminator. In a subsequent study by the same group that used a larger patient sample size and a longer follow-up period, FPG level also was shown to be a strong predictor of 2-year mortality and left ventricular systolic function after AMI. In addition, FPG added significantly to the discriminating ability of the Global Registry of Acute Coronary Events risk score (a validated tool used to estimate all-cause mortality risk in patients with acute coronary syndromes).²⁵ Our study demonstrates an independent graded relationship between elevated admission FPG levels and increasing in-hospital and 3-year mortality, consistent with these studies. This higher risk of both in-hospital and 3-year mortality persisted after controlling for higher burden of comorbidities (such as prior myocardial infarction and hypertension) and greater disease severity (higher Killip class, higher peak creatine kinase and creatinine levels, and lower ejection fraction) observed in patients with elevated FPG levels.

The prognostic relevance of hypoglycemia after AMI is controversial. Svensson et al²⁶ conducted a study in 713 diabetic patients with unstable angina or non-Q-wave

myocardial infarction and found a significantly higher mortality rate at 2 years in individuals with hypoglycemia (admission glucose level, ≤ 54.0 mg/dL) than in those with euglycemia; however, a causal link between in-hospital hypoglycemia and clinical outcomes ascertained 2 years later was difficult to establish. Kosiborod et al²⁷ showed that hypoglycemia (admission glucose level, < 59.5 mg/dL) was associated with increased mortality in patients with AMI, but this risk was confined to patients who had spontaneous hypoglycemia (ie, not including iatrogenic hypoglycemia). A more recent analysis by Goyal et al²⁸ revealed that both admission and postadmission hypoglycemia (admission glucose level, ≤ 68.5 mg/dL) could predict 30-day death in AMI patients. However, only hypoglycemia on admission predicted death, and this relationship dissipated after admission. Another report from the DIGAMI 2 (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction 2) trial²⁹ showed that hypoglycemia (admission glucose level, < 54.0 mg/dL) during the initial hospitalization was not an independent risk factor for future morbidity or mortality in patients with type 2 DM and myocardial infarction. However, hypoglycemic episodes were more prevalent in patients at high risk for other reasons. All of these trials used a much lower threshold to define hypoglycemia, and nondiabetic individuals were not included in some trials.²⁶⁻²⁹ In the current study, we observed that mild to moderately low FPG levels (≤ 90.0 mg/dL) were associated with a relative increase in mortality risk. There was a U-shaped relationship between admission FPG level and in-hospital and 3-year mortality. The latter result adds to the ongoing debate regarding admission plasma glucose level in patients presenting with AMI.

THE EFFECT OF ABNORMAL FPG LEVELS ON ALL-CAUSE MORTALITY IN MALE VS FEMALE PATIENTS WITH AMI

Hypoglycemia and hyperglycemia can both increase mortality. Clinical characteristics, management, and outcomes vary by sex; however, no previous study has investigated the effect of an abnormal FPG level on mortality in male vs female patients with AMI. We found that FPG-associated mortality did not vary significantly by sex in patients with AMI, even after adjustment for confounding factors. In both men and women, hypoglycemia and hyperglycemia were associated with higher in-hospital and 3-year all-cause mortality rates compared with euglycemia, and abnormal FPG level did not have a stronger effect on mortality in female than in male patients with AMI.

MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN HYPERGLYCEMIA OR HYPOGLYCEMIA AND HIGHER MORTALITY

Prior physiologic studies showed that higher glucose levels in patients with AMI were associated with higher free

fatty acid concentrations (which may induce cardiac arrhythmias), insulin resistance, and impaired myocardial glucose use, thus increasing the consumption of oxygen and potentially worsening ischemia.³⁰ Hyperglycemia also has been associated with microvascular dysfunction,³¹ a prothrombotic state,³² vascular inflammation,³³ endothelial dysfunction,³⁴ and generation of reactive oxygen species.³⁵ All of these mechanisms may potentiate tissue injury in the setting of AMI. Hypoglycemia and rapid changes in blood glucose level have been shown to increase levels of counterregulatory hormones, such as epinephrine and norepinephrine, which may induce vasoconstriction and platelet aggregation, resulting in ischemia.³⁶ Furthermore, in the presence of hypokalemia and raised serum catecholamine levels, which often simultaneously present during hypoglycemia, cardiac repolarization could be sufficiently prolonged to induce cardiac arrhythmias.³⁷

STUDY LIMITATIONS

Our study has several possible limitations. First, given the retrospective nature of the analysis, residual unmeasured confounding factors cannot be entirely excluded, and whether hyperglycemia and hypoglycemia are markers or mediators of death cannot be definitively determined in this observational study. Second, we were not able to determine how many patients with unrecognized DM before admission were diagnosed as having DM after discharge. Finally, although causes of in-hospital death could be classified as cardiac and noncardiac death, during follow-up some patients died out of the hospital, and we could not determine the accurate causes of death.

CONCLUSION

An increased FPG level was associated with a relatively higher risk of in-hospital mortality in men but not in women. Nonetheless, increased and decreased admission FPG levels could predict higher mortality rates regardless of sex. There was a striking U-shaped relationship between FPG levels and in-hospital and 3-year mortality. The impact of an abnormal FPG level on outcomes among older patients with AMI did not vary significantly by sex.

We thank Roberto Patarca, MD, for revising the manuscript.

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