Admission Plasma Glucose

An independent risk factor in nondiabetic women after coronary artery bypass grafting

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OBJECTIVE — To investigate the relationship between admission plasma glucose and 30-day mortality after primary isolated coronary artery bypass grafting (CABG) in nondiabetic patients.

RESEARCH DESIGN AND METHODS — All nondiabetic patients with admission plasma glucose measurement undergoing primary isolated CABG from 1993 to 1997 were included in this study.

RESULTS — In 878 consecutive patients (155 women), overall mortality was 3.4% (95% CI 2.3–4.8). The mortality rate in women (n = 11; 7.1%, 3.6–12.3) was higher than in men (n = 19; 2.6%, 1.6–4.1) (P = 0.01). There was a positive correlation between plasma glucose and 30-day mortality among women only (P = 0.0001). There was a higher mortality rate in the upper two glucose quartiles (11.7%, 5.5–21.0) compared with the lower two quartiles (2.6%, 3.0–8.9) in the female patients (P = 0.03); a plasma glucose of 6.0 mmol/l separated high- and low-mortality groups. Furthermore, women in the upper two glucose quartiles had a fourfold higher mortality rate than men in the similar quartiles (P = 0.002). Among men, there was no difference in mortality rate across glucose quartiles. In a multivariate analysis, admission plasma glucose, history of thyroid disease, left ventricular ejection fraction <0.35, operation bypass time, and perioperative myocardial infarction were independently associated with mortality.

CONCLUSIONS — Women with admission plasma glucose ≤6.0 mmol/l and men across the whole range of glucose values had similar mortality rates after CABG. The surplus female mortality was found only in subjects with plasma glucose >6 mmol/l. Further studies are needed to appraise the possible influence of glucose status on outcome from CABG in nondiabetic subjects.

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The relationship between diabetes and high mortality and morbidity after coronary artery bypass grafting (CABG) is well established (1,2). A relationship also exists between high admission plasma glucose levels and in-hospital mortality from acute myocardial infarction in diabetic patients (3,4). Recent studies have, furthermore, shown higher myocardial infarction mortality in nondiabetic subjects with high admission plasma glucose (5,6). To our knowledge, no study has been conducted to examine a relationship between glycemic state and CABG mortality in nondiabetic subjects. Therefore, we examined the possible relationship between admission plasma glucose and outcome in nondiabetic patients undergoing first-time isolated CABG.

RESEARCH DESIGN AND METHODS

— All nondiabetic patients admitted to the Cardiothoracic Surgery Unit, Hammersmith Hospital between January 1993 and December 1997 and undergoing primary isolated CABG were eligible for this study. Patient data were entered into a database at admission, and operative data were entered at the time of operation. Admission plasma glucose was measured by the colorimetric glucose oxidase method. All data were validated after computer entry by one of the investigators (D.Z.). The clinical information included age, gender, angina status according to the Canadian Cardiovascular Society classification, previous myocardial infarction ≤4 weeks before CABG, congestive heart failure, respiratory disease (chronic obstructive/nonobstructive lung disease, and tuberculosis), smoking, hypertension, other vascular (peripheral/cerebrovascular) disease, thyroid disease, BMI, impaired renal function (serum creatinine ≥150 μmol/l), left ventricular ejection fraction, number and type of diseased coronary arteries (>50% stenosis), operative priority (elective, urgent), cardiogenic shock before the operation, and drug treatment. Furthermore, we registered the occurrence of perioperative adverse events and length of hospital stay. The primary end point was 30-day mortality. Patients were excluded from the study if they, at any time during their hospital stay, received treatment for diabetes.

Operation procedure

Anesthesia was induced by intravenous administration of barbiturates and opiates (thiopentone and fentanyl), followed by pancuronium and continued with nitrous oxide and intermittent administration of volatile anesthesia. The perfusion circuit included a BARD 5700 Oxygenator (Bard William Harvey, Tewksbury, CT), and the perfusion was pulsatile. Myocardial protection was performed according to the surgeons' preference by cold crystalloid (standard St. Thomas' solution) cardioplegia, cold blood cardioplegia, or intermittent aortic cross-clamping and ventricular fibrillation at a moderate mean core hypothermia of 32.4°C. Use of the internal mammary artery as a conduit was standard procedure.

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Abbreviations: CABG, coronary artery bypass grafting.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient characteristics by sex and plasma glucose quartiles*

	Men			Women		
	Quartile 1–2	Quartile 3–4	Q1–2 vs. Q3–4 (*P*)	Quartile 1–2	Quartile 3–4	Q1–2 vs. Q3–4 (*P*)
n	362	361		78	77	
Age (years)‡¶	60 ± 10	62 ± 9	0.0005	64 ± 8	66 ± 7	0.1
Angina pectoris CCS III & IV†¶	120 (33)	130 (36)	0.4	38 (49)	47 (61)	0.1
Plasma glucose (mmol/l)	5.3 ± 0.5	7.3 ± 1.4	<0.0001	5.4 ± 0.5	7.5 ± 1.5	<0.0001
Congestive heart failure	26 (7.2)	49 (14)	0.005	9 (12)	17 (22)	0.08
Hypertension treatment‖	144 (40)	143 (40)	0.9	34 (44)	43 (56)	0.1
Thyroid disease‡¶	10 (2.8)	5 (1.4)	0.2	9 (12)	6 (7.8)	0.4
Myocardial infarction ≤4 weeks	20 (5.5)	28 (7.8)	0.05	3 (3.8)	10 (13)	0.1
Vascular disease§	34 (9.4)	41 (11)	0.4	6 (7.7)	16 (21)	0.02
Serum creatinine ≥150 μmol/l	14 (3.9)	31 (8.6)	0.009	3 (3.8)	7 (9.1)	0.2
Smoking†¶	262 (72)	246 (68)	0.2	43 (55)	35 (46)	0.2
Respiratory disease§	37 (10)	35 (9.7)	0.5	13 (17)	15 (20)	0.9
BMI ≥30	54 (15)	48 (13)	0.5	16 (21)	10 (13)	0.2
Urgent operative priority	8 (2.2)	12 (3.3)	0.4	5 (6.4)	1 (1.3)	0.1
Cardiogenic shock	3 (0.8)	2 (0.6)	0.7	0	0	
Ejection fraction						
Good >50%	220 (61)	184 (51)	—	52 (67)	43 (58)	—
Fair ≥35–50%	103 (28)	127 (35)	—	21 (27)	25 (32)	—
Poor <35%	39 (11)	50 (14)	0.2	5 (6.4)	9 (12)	0.3
Number of narrowed coronary arteries	2.7 ± 0.5	2.8 ± 0.5	0.1	2.7 ± 0.5	2.9 ± 0.4	0.09
Main stem stenosis	4 (0.1)	5 (0.1)	0.7	0	1 (1.3)	
Beta blocker*	210 (58)	210 (58)	0.9	35 (45)	41 (53)	0.3
Calcium antagonist	214 (59)	213 (59)	0.9	50 (64)	43 (56)	0.3
Nitrate	204 (56)	228 (63)	0.06	47 (60)	55 (71)	0.1
Corticosteroid	7 (1.9)	8 (2.2)	0.8	2 (2.6)	5 (6.5)	0.2

Data are means ± SD or *n* (%) of patients. Men versus women in quartiles 1–2: **P* <0.05; †*P* < 0.01; ‡*P* < 0.001. Men versus women in quartiles 3–4: §*P* <0.05; ‖*P* < 0.01; ¶*P* < 0.001. CCS, Canadian Cardiovascular Society; Q, quartile.

Statistical analysis

The subjects were stratified into quartiles based on plasma glucose level. Comparisons were performed using the χ^2 test, Mann-Whitney *U* test, or Kruskal-Wallis test as appropriate. Binomial exact CIs for mortality were calculated using one sample Student's *t* test of proportion and Fisher's exact test for independent groups. Correlations were determined by Spearman's rank test. Univariate logistic regression tests were used for analysis of predictors of mortality, and statistically significant variables were included in a multiple logistic regression analysis. The likelihood-ratio test and goodness-of-fit by Hosmer-Lemeshow χ^2 test were used to test the model. All analyses were conducted using the STATA statistics software package (Timberlake Consultants, Kent, U.K.). A two-tailed $P < 0.05$ was considered statistically significant, and values were corrected by the Bonferroni method.

RESULTS — A cohort of 1,465 nondiabetic patients was eligible for the study. However, 181 foreign patients were lost to 30-day follow-up, 395 had no admission plasma glucose measurement, and 11 patients (2 taking corticosteroids and 3 taking diuretics) were treated with insulin after the operation. A total of 878 patients (155 women) remained for inclusion in this study. Six patients (four men) who had glucose values >11.0 mmol/l at admission were receiving intravenous fluids, including glucose.

Clinical characteristics

Clinical characteristics of the patients studied, stratified by gender and glucose quartiles, are shown in Table 1 and Fig. 1. The women were older and had a higher prevalence of severe angina pectoris and history of thyroid disease than the men. The men had a higher prevalence of smoking than the women. Women in the upper two glucose quartiles had a higher prevalence of hypertension, vascular disease, and respiratory disease than men in the similar quartiles. There was no difference between men and women regarding glucose level, prevalence of heart failure, myocardial infarction, kidney dysfunction, obesity, operative priority, cardiogenic shock, left ventricular function, degree of coronary artery disease, and treatment with β-adrenergic blockers, vasodilators, and corticosteroids, with the exception that in the lower glucose quartiles, more men than women were taking β-adrenergic blockers. Women in the upper two glucose quartiles had a higher prevalence of vascular disease than women in the lower two quartiles. Plasma glucose correlated positively to age ($P < 0.0001$), serum creatinine level ($P < 0.003$), days in intensive care unit ($P = 0.008$), and total hospital stay ($P < 0.01$). Plasma glucose levels were higher in the heterogenous group of patients with heart failure, recent myocardial infarction, cardiogenic shock, and/or urgent operative priority (6.7 ± 1.7 mmol/l, $n = 172$) than in the remaining patients (6.3 ± 1.4 mmol/l, $n = 706$) ($P = 0.001$).

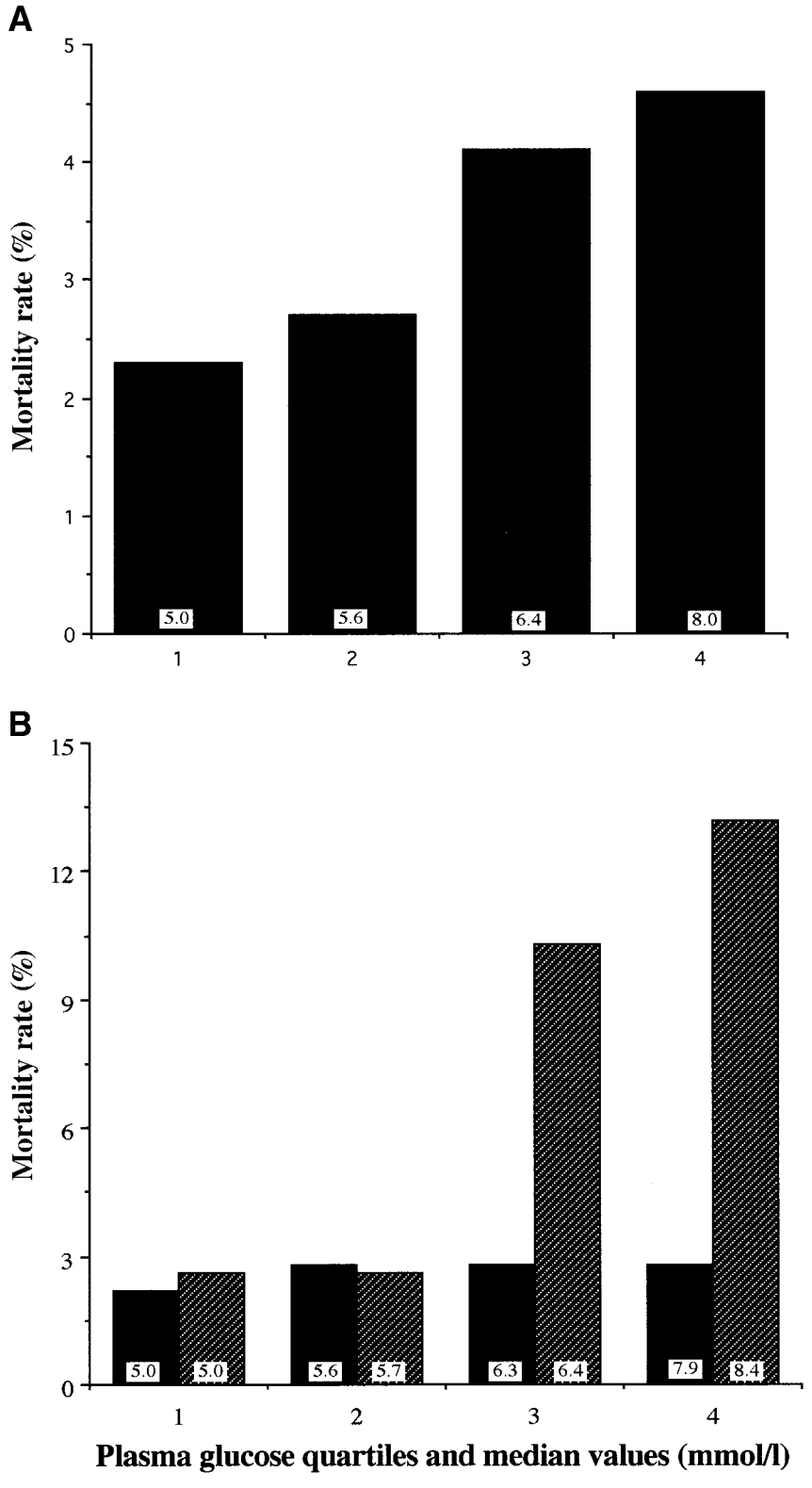

Figure 1—*Relationship between plasma glucose quartiles and mortality overall* (A) *and in men* (■) *and women* (□) (B).

Operation characteristics

There were no significant inter–glucose quartile differences concerning the number of graft anastomoses ($P = 0.5$), type of myocardial preservation ($P = 0.8$), bypass time ($P = 0.1$), aortic cross-clamp time ($P = 0.2$), reoperation for bleeding ($P = 0.9$), or perioperative myocardial infarction ($P = 0.9$). The left internal mammary artery was used as a conduit in 95% of patients, and the right internal mammary artery was used in 4.5% of all patients; no difference was noted between women and men ($P = 0.2$). Aortic cross-clamp time did not differ between men (41.6 ± 16.7 min) and women (39.2 ± 16.0 min) ($P = 0.1$). Men and women had a similar number of graft anastomoses (3.3 ± 0.8 and 3.2 ± 0.8, respectively) ($P = 0.07$). Significantly more women (14.8%) required postoperative intravenous inotropic support than men (11.8%) ($P = 0.03$). The perioperative myocardial infarction rate in women ($n = 4$) did not differ from that ($n = 7$) in men ($P = 0.1$).

Mortality

In the entire group of patients studied, a total of 30 deaths occurred (3.4%, 95% CI 2.3–4.8), and a significant correlation was seen between plasma glucose level and 30-day mortality ($P = 0.03$). There was, furthermore, a tendency toward increasing mortality across the glucose quartiles; 5 (2.3%, 0.7–5.2), 6 (2.7%, 1.0–5.8), 9 (4.1%, 1.9–7.6), and 10 (4.6%, 2.2–8.3) deaths occurred in the first through fourth quartiles, respectively ($P = 0.1$) (Fig. 1*A*). A positive correlation was noted between admission plasma glucose and 30-day mortality among women ($P = 0.0001$), as well as a trend to a correlation among men ($P = 0.05$). Mortality of 11 women (7.1%, 3.6–12.3) was higher than mortality of 19 men (2.6%, 4.1–11.6) ($P = 0.01$). Among the women, there was a higher mortality rate in the upper two glucose quartiles (9 patients, 11.7%, 5.5–21.0) compared with the lower two quartiles (2 patients, 2.6%, 3.0–8.9) ($P = 0.03$) (Figs. 1*B* and 2); a glucose value of 6.0 mmol/l separated the upper two and lower two glucose quartiles. Women in the upper two glucose quartiles had a fourfold higher mortality rate than men in similar glucose quartiles ($P = 0.002$) (Fig. 1*B*). A total of 25 patients (9 women) died of a cardiac disorder, and the remaining 5 patients died of septicemia or stroke. Inclusion of cardiac deaths only in the analysis did not change the findings. Thus, there was a positive correlation between cardiac mortality and plasma glucose among women ($P = 0.003$) but not among men ($P = 0.4$). Mortality in women in the upper two glu-

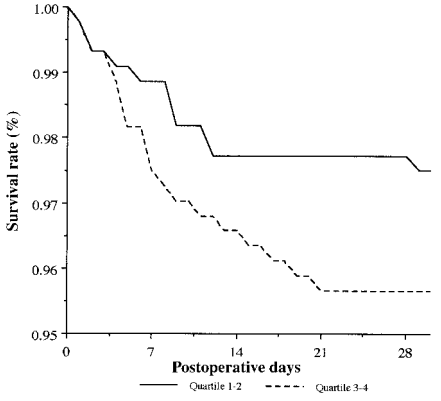

Figure 2—*Survival rate in women by plasma glucose quartiles 1–2 and 3–4* (P = *0.03*).

cose quartiles was higher than mortality among men in the similar quartiles (P = 0.001) and among women in the lower quartiles (P = 0.01). Among the most sick and high-risk patients (congestive heart failure, recent myocardial infarction, cardiogenic shock, and/or urgent operative priority) in the upper two glucose quartiles (n = 103), the mortality rate was fivefold higher in women (19.2%) than in men (3.9%) (P = 0.01). In the remaining patients in the upper two glucose quartiles (n = 335), the mortality rate was threefold higher in women (7.8%) than in men (2.5%) (P = 0.047). There was no difference between men and women with respect to glucose levels within these groups.

Multiple logistic regression analysis

Ten preoperative and operative variables that predicted mortality in the univariate analysis were included in the multivariate analysis (Table 2). Angina status (a subjective parameter) and cardiogenic shock (<0.6% of the patients) were not included in the analysis. Plasma glucose, a history of thyroid disease, left ventricular ejection fraction <0.35, operative bypass time, and perioperative myocardial infarction were independently associated with mortality. Interaction was found between gender and plasma glucose level (odds ratio 1.518 [1.001–2.301], P = 0.050) in relation to mortality, and there was no indication of confounding between these two variables (Table 1). No interaction was found between gender and the other variables.

CONCLUSIONS — We found a positive correlation between admission plasma glucose and 30-day mortality in nondiabetic patients undergoing primary isolated CABG. Overall, there was a trend to a graded relationship between glucose levels and mortality that was present even in the lowest glucose quartiles, in which the values were below the fasting glucose criteria for the diagnosis of impaired glucose tolerance (7) (Fig. 1*A*). The mortality rate was several-fold higher among women in the third and fourth glucose quartiles compared with men in the identical quartiles and with women in the lower quartiles (Fig. 1*B*). A cutoff level of ~6 mmol/l seemed to exist among glucose values in the women, above which mortality increased considerably, whereas among men, there was no consistent increase in mortality across the whole range of glucose values. In women, the mortality rate in the upper two quartiles started to diverge from that in the lower two quartiles from the fourth postoperative day and continued to do so for up to 3 weeks after the operation (Fig. 2). Women in the upper glucose quartiles had a higher prevalence of other vascular disease than women in the lower quartiles (Table 1). This alone cannot explain the marked difference in mortality between these quartiles. The patients in the upper glucose quartiles undoubtedly include individuals with and without impaired glucose tolerance or insulin resistance and possibly a minority with diabetes. In some of these patients, hyperglycemia is likely to be the consequence of increased endocrine-metabolic activity in response to pain or stress (8) or myocardial damage (9) or due to the patients being nonfasting or, in a few cases, on glucose infusion. However, we excluded patients who needed antidiabetic treatment after the operation.

Influence of gender

Although women generally had a higher prevalence of severe angina pectoris, hypertension, thyroid disease, vascular disease, and respiratory disease than men (Table 1), there were no major differences between the two sexes with respect to recognized core variables (priority of operation, left ventricular function, left main coronary artery disease, and number of diseased coronary arteries) predicting CABG mortality (10), except that women were, on average, 4 years older than men. It is generally recognized that women have higher CABG mortality than men, as found in the present study (11,12). Several reasons have been suggested to explain this difference: coronary arteries in women have been reported to be of smaller caliber, which could result in more technical difficulties during operation; internal mammary arteries have been less frequently used in women; and a referral bias exists, as women are considered for surgery at a later stage of disease and at an older age than men (10–12). However, in the present study, coronary artery calibers caused no additional operative problems in women, because men and women had identical aortic cross-clamp times despite having the same number of vessels grafted. Furthermore, there were no differences with respect to number and type of diseased coronary vessels or to the use of internal mammary

Table 2—*Independent predictors of mortality in nondiabetic patients*

Variable	*n*	Odds ratio	*P*	(95% CI)
Bypass time	878	1.017	0.002	(1.006–1.027)
Glucose	878	1.385	0.001	(1.152–1.665)
Gender				
Male	723	1		
Female	155	2.289	0.064	(0.954–5.398)
Election fraction <35				
No	775	1		
Yes	103	2.939	0.025	(1.148–7.526)
Thyroid disease				
No	848	1		
Yes	30	5.048	0.021	(1.270–20.082)
Perioperative myocardial infarction				
No	867	1		
Yes	11	53.794	<0.001	(13.006–222.498)

artery conduits between men and women, and glucose level was more important than age as an independent predictor of operative mortality in the multivariate analysis. Interaction was found only between gender and plasma glucose with respect to mortality. Female gender is among independent risk factors for 30-day post-CABG mortality unique to diabetic patients (13). The present study suggests a similarly enhanced vulnerability in nondiabetic women in the upper glucose quartiles.

Metabolic interactions

Low glucose levels most likely reflect a favorable insulin/glucose interaction (7). In insulin-sensitive individuals, insulin increases muscular flow in a dose-dependent manner and simultaneously augments glucose metabolism (14). Cardiac glucose oxidation results in a more efficient myocardium with improved contractility (15,16). Furthermore, increased myocardial glucose supply increases myocyte resistance to toxic effects of intracellular release of calcium during hypoxia (15,16). Insulin not only lowers glucose levels, it also decreases arterial levels of free fatty acids and, thereby, myocardial uptake of free fatty acids (17). In contrast, hyperglycemia is found in insulin deficiency and insulin-resistant states and is associated with increased lipolytic activity and high circulating levels of free fatty acids (15,18). Fasting, the surge in sympathetic activity, and the administration of catecholaminergic drugs and heparin during cardiac surgery further increase circulating free fatty acids (15,19). In the myocardium, excess fatty acids and their intermediates may increase ischemic damage and oxygen requirements, generate arrhythmias, and diminish glucose utilization (15,16).

Other risk factors

Operative bypass time, history of thyroid disease, left ventricular ejection fraction <0.35, and perioperative myocardial infarction were the only other significant mortality predictors in the present study. The importance of three of these factors is well known, whereas the fact that patients with a history of thyroid disease had a fivefold increased mortality risk is a new and intriguing observation. It could be related to some degree of persistent cardiomyopathy, even after successful treatment of the thyroid disease (20). Thus, cardiac functional and structural abnormalities may exist in patients on standard fixed therapy for thyroid disease (21). The fact that the prevalence of thyroid disease was identical in the lower and higher glucose quartiles of the female group makes confounding between these endocrine variables unlikely in relation to the outcome of this study. Accordingly, a history of thyroid disease and glucose level were both independently associated with mortality (Table 2). The reason that well-known risk factors such as age and renal function predicted mortality in the univariate, but not in the multivariate analysis, was probably the fact that glucose was a stronger predictor in the multivariate analysis.

Limitations and conclusions

There are several limitations to the present study. The size of the study population resulted in relatively few deaths after CABG. We used only one baseline glucose measurement to classify patients into glucose quartiles. We used admission values, which might not have been taken in the fasting state. We must assume, however, that nonfasting patients have been evenly distributed among men and women. The likely presence of nonfasting patients with normal glucose tolerance in the upper quartiles may even have weakened an association between mortality and an abnormal glycemic state. Some of the patients in the highest glucose quartile were seriously ill and were treated with glucose infusion. Others were distressed and in pain and required urgent revascularization (Table 1). However, this was the case for both men and women. The fact that mortality was higher in women than in men in both the most sick/high-risk patients and patients at normal risk in the upper glucose quartiles suggests that elevated glucose level is associated, at least in part, with increased mortality in women.

In the present study, we used a simple estimate of the general metabolic state (i.e., a single glucose measurement). It showed, however, that outcome from a cardiac ischemic event (CABG) was independently related to admission plasma glucose level. There was an increasing total and cardiac mortality rate in relation to glucose level among women. A plasma glucose cutoff value of 6.0 mmol/l separated women with high and low mortality rates. It was an unexpected finding that elevated plasma glucose, as a marker of impaired glucose metabolism, was of importance only in women. Whether this can explain the excess mortality in nondiabetic women undergoing CABG must be confirmed in larger studies with more thorough testing of glucose metabolism.

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