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CLINICAL STUDIES

MYOCARDIAL INFARCTION

Angiographic Findings and Outcome in Diabetic Patients Treated With Thrombolytic Therapy for Acute Myocardial Infarction: The GUSTO-I Experience

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Objectives. **This study sought to determine whether diabetes mellitus, in the setting of thrombolysis for acute myocardial infarction, affects 1) early infarct-related artery patency and reocclusion rates; and 2) global and regional ventricular function indexes. We also sought to assess whether angiographic or baseline clinical variables, or both, can account for the known excess mortality after myocardial infarction in the diabetic population.**

Background. **Mortality after acute myocardial infarction in patients with diabetes is approximately twice that of nondiabetic patients. It is uncertain whether this difference in mortality is due to a lower rate of successful thrombolysis, increased reocclusion after successful thrombolysis, greater ventricular injury or a more adverse angiographic or clinical profile in diabetic patients.**

Methods. **Patency rates and global and regional left ventricular function were determined in patients enrolled in the GUSTO-I Angiographic Trial. Thirty-day mortality differences between those with and without diabetes were compared.**

Results. **The diabetic cohort had a significantly higher proportion of female and elderly patients, and they were more often hypertensive, came to the hospital later and had more congestive heart failure and a higher number of previous myocardial infarctions and bypass surgery procedures. Ninety-minute patency (Thrombolysis in Myocardial Infarction [TIMI] flow grade 3) rates in patients with and without diabetes were 40.3% and 37.6%, respectively ($p = 0.7$). Reocclusion rates were 9.2% vs. 5.3% ($p = 0.17$). Ejection fraction at 90 min after thrombolysis was similar in diabetic and nondiabetic patients ([mean ± SEM] 61.0 ± 1.6% vs. 60.1 ± 0.7%, $p = 0.7$), as was regional ventricular function (number of abnormal chords: 19.1 ± 2.0 vs. 17.5 ± 0.8, $p = 0.3$; SD/chord: −2.3 ± 0.2 vs. −2.4 ± 0.1, $p = 0.6$). Diabetic patients had less compensatory hyperkinesia in the noninfarct zone (SD/chord: 1.3 ± 0.2 vs. 1.7 ± 0.1, $p \leq 0.01$). No significant difference in ventricular function was noted at 5- to 7-day follow-up. The 30-day mortality rate was 11.3% in diabetic versus 5.9% in nondiabetic patients ($p \leq 0.0001$). After adjustment for clinical and angiographic variables, diabetes remained an independent determinant of 30-day mortality ($p = 0.02$).**

Conclusions. **Early (90-min) infarct-related artery patency as well as regional and global ventricular function do not differ between patients with and without diabetes after thrombolytic therapy, except for reduced compensatory hyperkinesia in the noninfarct zone among patients with diabetes. Diabetes remained an independent determinant of 30-day mortality after correction for clinical and angiographic variables.**

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Diabetes is a risk factor for coronary artery disease and is associated with increased mortality in the setting of acute myocardial infarction (1–7). However, the etiology of this excess mortality remains to be defined. Patients with diabetes generally have a greater number of indicators of an adverse clinical prognosis, such as previous myocardial infarction (8,9) and congestive heart failure (10–12), and may be older (13,14) and have more multivessel coronary artery disease (10,15) than nondiabetic patients. Other potential mechanisms responsible for the excess mortality in diabetic patients may include 1) decreased rates of successful early thrombolysis or lower rates of sustained patency; 2) increased myocardial injury in response to ischemia/reperfusion; 3) a greater degree of diastolic left ventricular dysfunction; or 4) increased adverse outcome after revascularization procedures.

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I)

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CI	=	confidence interval
GUSTO-I	=	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
IV	=	intravenous
OR	=	odds ratio
SC	=	subcutaneous
TIMI	=	Thrombolysis in Myocardial Infarction
t-PA	=	tissue-type plasminogen activator

Angiographic Study (16) offered the unique opportunity to assess the clinical and angiographic determinants of outcome in patients with diabetes who had an acute myocardial infarction and to provide possible explanations for the mechanisms responsible for the excess mortality associated with diabetes. The specific purpose of this study was to investigate the secondary hypothesis that diabetes has an effect on early and sustained infarct-related artery patency or global and regional left ventricular function, or both, in response to ischemic injury and subsequent reperfusion after acute myocardial infarction.

Methods

Study patients. The GUSTO Angiographic Study (16) has been described in detail previously. Briefly, patients were included in the GUSTO trial if they had chest pain <6 h in duration and ST segment elevation in at least two contiguous leads. We determined differences in global and regional left ventricular function after thrombolysis in diabetic and nondiabetic patients who had angiographically documented patency (Thrombolysis in Myocardial Infarction [TIMI] flow grades 2 and 3) in the infarct-related coronary artery 90 min (±45) after thrombolytic therapy, sustained patency at 5- to 7-day follow-up angiography and ventriculograms adequate for analysis. We compared noninfarct zone function at 90 min in all diabetic and nondiabetic patients randomized to 90-min angiography with adequate ventriculograms for analysis regardless of 90-min TIMI flow grade.

Thrombolytic therapy and coronary angiography. As described previously (17), patients were randomized to one of four thrombolytic regimens. At the time of drug randomization, patients were also randomized to one of four times for initial coronary angiography after the start of thrombolytic therapy. This report includes angiographic data from those patients randomized to 90-min postthrombolytic therapy catheterization. These patients were also scheduled to undergo 5- to 7-day follow-up catheterization.

Core angiographic laboratory procedures and cineangiographic analysis. Films were interpreted by an experienced angiographer (C.F.L., J.S.R., A.M.R.) who had no knowledge of treatment allocation, angiographic randomization or diabetic status. Infarct-related artery patency, as defined by TIMI flow grade, was assessed according to standard methods (18). Ventriculographic silhouettes were acquired digitally at end-systole and end-diastole, and the borders were defined by the core laboratory angiographer (C.F.L., J.S.R., A.M.R.). Ventricular volumes and ejection fraction were calculated by the area–length method (19). Regional ventricular function was assessed by the method of Bolson et al. (20) and included mean excursion of the most abnormal 50% of chords in the infarct region, expressed as the number of standard deviations per chord (SD/chord), and the number of consecutive chords in the infarct region >2 SD below the norm (number of chords). The noninfarct region was similarly assessed as the SD/chord of the most normal 50% of chords. Patients who underwent coronary angioplasty were excluded from analysis of ventricular function.

Definition of diabetes. *Diabetes* was defined as an a priori condition if the patient identified himself/herself as diabetic and was receiving standard therapy (oral hypoglycemic agents or insulin) for diabetes at the time of admission to the trial. The number of insulin-dependent diabetics patients in this cohort was insufficient to be analyzed as a separate subgroup.

Rescue angioplasty definition. Patients with TIMI flow grade 0 or 1 in the infarct-related artery at the time of 90-min catheterization or who had reocclusion of an initially patent (TIMI flow grade 2 or 3) infarct-related artery and underwent immediate attempted angioplasty with cine films adequate for analysis were classified as patients with a *rescue angioplasty attempt*. *Successful rescue angioplasty* was defined as conversion from TIMI flow grade 0 or 1 to 2 or 3 and <50% residual stenosis at the completion of the angioplasty procedure.

Statistical analysis. Results are expressed as mean value ± SEM, unless otherwise stated. Chi-square analysis was used to compare categoric data, and continuous variables were compared using the unpaired Student *t* test (two-tailed). Multivariable linear regression analysis (21) was used to determine the independent effect of clinical and angiographic variables in the prediction of regional and global left ventricular function indexes. The relation between diabetes and mortality was analyzed by multivariable logistic regression analysis (21). Demographic and angiographic variables that were considered to be possibly related to left ventricular functional outcomes or mortality, or both, were incorporated into the model, and the independent effect of diabetes was determined. Clinical variables for testing were chosen on the basis of their previously described independent effect on 30-day mortality (22) and included diabetes, age, gender, previous history of infarction and initial heart rate and systolic blood pressure at time of study entry. Angiographic variables included 90-min TIMI flow grade and the presence of multivessel coronary artery disease. The TIMI flow grade was entered as a dichotomous variable (TIMI 0, 1 or 2 vs. TIMI 3) to reflect its biologic significance (16). Continuous variables were entered into the model without modification except as previously stated. Relative odds ratios were also determined with 95% confidence intervals for 30-day mortality for diabetic and nondiabetic patients with and without adjustment for clinical and angiographic variables. A

Table 1. Baseline Variables and Outcomes in 2,431 GUSTO Angiographic Study Patients

	Diabetes	No Diabetes	p Value
Age (yr)	65 (55, 71)	61 (51, 69)	
Age ≥75 yr	15.0	11.0	0.049
Male	67.1	79.2	≤0.001
Smoker	60.0	73.0	0.1
Body weight (kg)	80 (71, 92)	77 (68, 87)	
Hypertension	53.1	34.0	≤0.001
Previous CABG	5.8	4.3	0.02
Hypercholesterolemia	39.0	34.0	0.08
Previous MI	18.4	13.0	≤0.01
Time to treatment (h)	3.2 (2.3, 4.4)	2.7 (2.0, 3.8)	
Anterior MI	39.5	38.0	0.6
No. of diseased vessels			
1	45.7	59.5	
2	32.0	25.1	≤0.0001
3	22.3	15.4	
CHF	22.0	14.2	≤0.001
Shock	7.5	6.0	0.3
Reinfarction	5.5	3.7	0.1
CABG (in hospital)	12.3	9.7	0.15
PTCA (in hospital)	39.6	34.3	0.06

Data presented are median (25th, 75th percentiles) for continuous variables or percent of patients in each category. CABG = coronary artery bypass surgery; CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

p value <0.05 was considered indicative of statistical significance in all cases.

Thirty-day cumulative survival differences between diabetics and nondiabetic patients was demonstrated by Kaplan-Meier curves. The significance of the difference was determined by the log-rank test.

Results

Patients. The GUSTO Angiographic Trial enrolled 2,431 patients. Patients with diabetes represented 12.8% (n = 310) of the cohort, and nondiabetic patients represented 87.2% (n = 2,116); the status of 5 patients was unknown with regard to diabetes. Among patients with diabetes, 26% were receiving insulin. Those with diabetes differed from nondiabetic patients with respect to multiple baseline clinical variables (Table 1): They were older, included a greater proportion of the elderly (age ≥75 years), were more often female and had significantly longer time to treatment from pain onset than nondiabetic patients. Patients with diabetes were also more often hypertensive, had a greater incidence of previous myocardial infarction and were more likely to develop congestive heart failure. Among patients randomized to 90-min angiography, differences in clinical variables between those with and without diabetes were similar to those of the entire angiographic trial population.

Similar proportions of diabetic and nondiabetic patients were randomized to each thrombolytic regimen: tissue-type plasminogen activator (t-PA) plus intravenous (IV) heparin, 26% versus 25%; streptokinase (IV and subcutaneous [SC] regimens combined) 42% versus 50%; t-PA plus streptokinase and IV heparin, 33% and 25% (Mantel-Haenszel chi-square 1.4, p = 0.2). Also, similar proportions of diabetic and nondiabetic patients with infarct-related artery patency (TIMI flow grade 2 or 3) by 90-min angiography were noted in each treatment group: t-PA plus IV heparin, 32.0% versus 30.0%; streptokinase (IV and SC groups combined), 34.0% versus 43.2%; t-PA plus streptokinase plus IV heparin, 35.0% versus 27.0% (Mantel-Haenszel chi-square 4.1, p = 0.12).

Table 2. Adjunctive Medical Therapy

	Diabetes	No Diabetes	p Value
In hospital			
Aspirin	98.1	99.1	0.09
CCB	35.7	27.8	0.004
ACEI	32.8	22.9	<0.0001
BB	47.9	44.4	0.24
Nitrates	83.8	79.9	0.11
At discharge			
CCB	26.8	20.6	0.02
ACEI	24.3	19.1	0.04
BB	59.4	63.9	0.13
Nitrates	38.4	35.6	0.36

Data presented are percent of patients in each category. ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; CCB = calcium channel blocker.

Adjunctive medical therapy. A similar proportion of patients with and without diabetes received aspirin during their hospital course (Table 2). Patients with diabetes were also as likely as those without diabetes to be treated with nitrates and beta-adrenergic blocking agents in the hospital (Table 2). Similar relations were noted between patients with and without diabetes regarding nitrate and beta-blocker usage at the time of hospital discharge. However, a significantly greater proportion of patients with diabetes received calcium channel blocking agents and angiotensin-converting enzyme (ACE) inhibitors during their hospital course and at the time of discharge (Table 2).

Patency and reocclusion of infarct-related artery. The 90-min postthrombolytic therapy patency rate (TIMI flow grades 2 and 3) was similar in diabetic and nondiabetic patients (70.1% vs. 66.6%, p = 0.7). Of note, the proportion of diabetic patients with TIMI flow grade 3 in the infarct-related artery was not significantly different from that for nondiabetic patients (Table 3).

Table 3. Diabetes and 90-Minute Angiographic Patency*

	TIMI Flow Grade		
	0–1	2	3
Diabetes	29.8 (43)	29.8 (43)	40.3 (58)
No diabetes	33.4 (311)	29.0 (270)	37.6 (350)

*Mantel-Haenszel chi-square 0.68, p = 0.6. Data presented are percent (number) of patients. TIMI = Thrombolysis in Myocardial Infarction.

Table 4. Quantitative Coronary Angiography 90-Minutes After Thrombolytic Therapy

	Diabetes	No Diabetes	p Value
% diam stenosis	77.8 (70.0, 100) (n = 147)	78.4 (68.4, 100) (n = 940)	0.7
% area stenosis	95.3 (91.0, 100) (n = 147)	95.4 (90.0, 100) (n = 940)	0.2
MLD (mm)	0.70 (0.44, 0.87) (n = 109)	0.73 (0.56, 0.99) (n = 657)	0.02
Mean normal diam (mm)* (reference segment)			
RCA	2.9 (2.6, 3.3) (n = 93)	3.2 (2.6, 3.5) (n = 573)	0.004
LCx	2.5 (2.1, 2.9) (n = 23)	3.0 (2.5, 3.3) (n = 182)	0.007
LAD	2.5 (2.0, 2.8) (n = 77)	2.7 (2.3, 3.0) (n = 512)	0.004

*Infarct-related artery reference segment data based on major epicardial vessel segments in all GUSTO angiographic study patients. Data presented are median (25th, 75th percentiles). Diam = diameter; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery.

Table 5. Global and Regional Left Ventricular Function in Diabetic and Nondiabetic Patients With a Patent (TIMI flow grade 2 or 3) Infarct-Related Artery*

	EF (%)	ESVI (ml/m^2)	No. of Chords	SD/ Chord
90 min after thrombolysis				
Diabetes	61.0 ± 1.6 (n = 56)	26.3 ± 1.8 (n = 48)	19.1 ± 2.0 (n = 56)	−2.3 ± 0.2 (n = 56)
No diabetes	60.1 ± 0.7 (n = 397)	27.2 ± 0.8 (n = 339)	17.5 ± 0.8 (n = 394)	−2.4 ± 0.1 (n = 394)
5–7 days after thrombolysis				
Diabetes	60.0 ± 1.7 (n = 58)	26.4 ± 2.1 (n = 48)	15.2 ± 1.9 (n = 58)	−2.0 ± 0.2 (n = 58)
No diabetes	60.0 ± 1.7 (n = 384)	28.2 ± 0.7 (n = 325)	17.5 ± 0.9 (n = 374)	−2.0 ± 0.1 (n = 380)

*$p > 0.05$ for all comparisons. Data presented are mean value ± SEM (number of patients). EF = ejection fraction; ESVI = end-systolic volume index; TIMI = Thrombolysis in Myocardial Infarction.

Seven hundred twenty-one patients (101 diabetic, 620 nondiabetic) had infarct-related artery patency (TIMI flow grade 2 or 3) at the time of 90-min angiography. Scheduled 5- to 7-day angiography confirmed patency in 481 of these 721 patients. Follow-up angiography was performed in 62 (61.4%) of 101 patients with diabetes and 419 (67.5%) of 620 nondiabetic patients (chi-square 0.3, p = 0.6). Two hundred forty patients (39 diabetic, 201 nondiabetic) did not undergo follow-up angiography for one of the following reasons: patient or physician refusal, intervening percutaneous transluminal coronary angiography, reocclusion of an initially patent vessel or follow-up angiography performed before the 5- to 7-day time period. Six (5.9%) of 101 diabetic and 13 (21%) of 620 nondiabetic patients with an initially patent infarct-related artery died before follow-up angiography (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.1 to 8.3). Reocclusion of an initially patent (TIMI flow grade 2 or 3) infarct-related artery occurred in 9.2% of diabetic versus 5.3% of nondiabetic patients (p = 0.17).

Quantitative coronary angiography. Percent diameter stenosis, percent area stenosis and minimal lumen diameter of the infarct-related artery at 90-min in diabetic and nondiabetic patients with patent vessels are shown in Table 4. Diabetic and nondiabetic patients exhibited similar percent diameter and percent area stenosis at early angiography. Diabetic patients had a significantly smaller minimal lumen diameter in the infarct-related artery than nondiabetic patients. Reference segment diameters in all infarct-related arteries were also significantly smaller in diabetic than nondiabetic patients. This difference remained true after adjustment for multiple clinical variables, including age, gender, hypertension, hypercholesterolemia and body surface area (p = 0.0002).

Procedure outcomes. Percutaneous transluminal coronary angioplasty was performed in 121 (39.0%) of 310 diabetic and 717 (33.8%) of 2,116 nondiabetic patients (p = 0.07) who were enrolled in the entire angiographic study. The mortality rate in patients with diabetes after angioplasty was 13.2% (16 of 121) compared with 4.5% (32 of 717) in nondiabetic patients (OR 3.3, 95% CI 1.7 to 6.4). Cineangiograms were available for analysis in 46 diabetic and 183 nondiabetic patients who underwent attempted rescue angioplasty. The mortality rate after attempted rescue angioplasty was 21.7% in diabetic versus 9.3% in nondiabetic patients (p = 0.02). Rescue angioplasty tended to be less successful in diabetic (36 [78%] of 46) than in nondiabetic patients (163 [89%] of 183), but the difference was of marginal statistical significance (p = 0.052). The 30-day mortality rate in diabetic patients who underwent successful rescue angioplasty was 8.3% (3 of 36) versus 8.0% (13 of 163) for nondiabetic patients (p = 0.9).

Elective angioplasty after myocardial infarction was attempted in 75 (24.2%) of 310 diabetic and 534 (25.2%) of 2,116 nondiabetic patients (p = 0.7). The 30-day mortality rate in diabetic patients undergoing elective angioplasty was 8.0% versus 2.2% in nondiabetic patients (OR 3.8, 95% CI 1.5 to 9.7).

Coronary artery bypass surgery was performed in 12.3% of diabetic and 9.7% of nondiabetic patients (p = 0.15). The 30-day mortality rates did not differ between diabetic (3 [7.9%] of 38) and nondiabetic patients (10 [4.9%] of 204) undergoing bypass surgery (p = 0.45).

Left ventricular function. Fifty-five percent of diabetic and 64% of nondiabetic patients had adequate studies for inclusion into the ventriculographic analysis (p = 0.1). Global and regional left ventricular functional indexes at 90 min and 5 to 7 days after thrombolysis are shown in Table 5. Regional ventricular function in the infarct-related artery territory improved in both diabetic and nondiabetic patients 1 week after thrombolysis, but there was no significant difference in ejection fraction, end-systolic volume index, number of chords in the infarct zone or regional function at either 90 min or 5 to 7 days

Table 6. Multivariable Analysis: Clinical and Angiographic Independent Determinants of Left Ventricular Global and Regional Function in Acute Myocardial Infarction

	90 Min After Thrombolysis				5–7 Days After Thrombolysis			
	EF (n = 1,051)	No. of Chords (n = 1,041)	SD/Chord (n = 1,046)		EF (n = 786)	No. of Chords (n = 776)	SD/Chord (n = 779)	
			MI Zone	Non-MI Zone			MI Zone	Non-MI Zone
Diabetes	0.38	0.98	0.57	0.035	0.89	0.36	0.68	0.58
TIMI flow grade (90 min)	0.0001	0.0001	0.0001		0.0003	0.0001	0.0001	
Anterior MI	0.0001	0.0001			0.0001	0.0001		
Previous MI				0.0001	0.0001			0.0001
Multivessel CAD				0.0001				0.0001

Data presented are p value for the independent variable. CAD = coronary artery disease; EF = ejection fraction; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

after thrombolysis. The diabetic and nondiabetic subgroups differed regarding size, with relatively fewer diabetic than nondiabetic patients. The power to detect a difference of five percentage points in ejection fraction, 8 ml/m^2 in end-systolic volume index, 8 chords or 0.6 SD/chord between diabetic and nondiabetic patients at the 0.05 level of significance for the number of patients shown in Table 4 in each group is 72%, 95%, 94% and 58%, respectively at 90 min after thrombolysis. The corresponding power to detect the same differences at 5- to 7-day follow-up ventriculography is 74%, 98%, 91% and 61%, respectively.

Noninfarct zone contractile function was also assessed at 90 min after thrombolysis regardless of infarct-related artery TIMI flow grade in 146 diabetic and 929 nondiabetic patients with ventriculograms adequate for analysis. Diabetic patients exhibited significantly less hyperkinesia in the noninfarct zone than nondiabetic patients (SD/chord 1.3 ± 0.2 vs. 1.7 ± 0.1, $p \leq 0.01$).

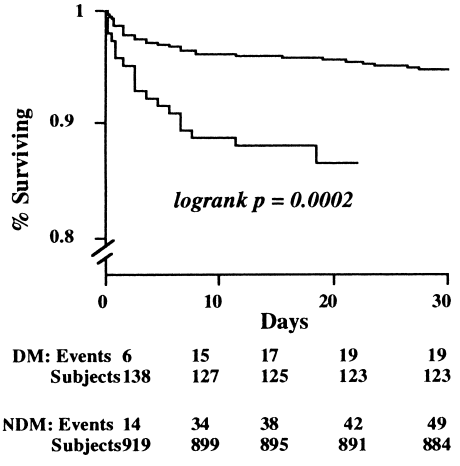
Multivariable analysis: left ventricular function. Diabetic and nondiabetic patients differed with regard to many demographic variables affecting global or regional left ventricular function. The independent effect of each of these variables on ventricular function was determined by multivariable linear regression analysis. Results (Table 6) show that whereas diabetes was a significant determinant of 90-min noninfarct zone function (reduced compensatory hyperkinesia), a history of previous myocardial infarction and the presence of multivessel coronary artery disease were the primary determinants of noninfarct zone function at this time point. However, at 5- to 7-day follow-up, diabetes did not exhibit an independent effect on noninfarct zone contractile function. In addition, diabetes was not an independent determinant of either early (90 min) or 5- to 7-day global or infarct-related regional left ventricular function after thrombolytic therapy.

Mortality. The unadjusted 30-day mortality rate in diabetic patients was 11.3% versus 5.9% in nondiabetic patients ($p \leq 0.0001$) (Fig. 1). The probability of death at 30 days was increased in diabetic compared with nondiabetic patients at all ages (Fig. 2). The mortality rate in diabetic patients with 90-min infarct-related artery patency (TIMI flow grade 2 or 3) was 11.9% versus 4.5% in nondiabetic patients (OR 2.9, 95% CI 1.4 to 5.8). The mortality rate in diabetic patients with TIMI 3 flow in the infarct-related artery at 90 min was 8.6% versus 3.4% in nondiabetic patients (OR 2.7, 95% CI 0.9 to 7.8). The mortality rate among diabetic patients treated with insulin was 17.7% versus 8.7% for those not receiving insulin (chi-square 4.9, p = 0.02). Figure 3 illustrates the effect of diabetes on 30-day mortality after adjustment for clinical or angiographic variables, or both. After adjustment for *angiographic variables*, diabetes remained a significant determinant of 30-day mortality (p = 0.006). After adjustment for *clinical variables*, diabetes also remained a predictor of 30-day mortality (p = 0.008). After adjustment for *both clinical and angiographic variables*, diabetes remained an independent determinant of 30-day mortality (p = 0.02). Of note, rescue and elective angioplasty were not independent determinants of 30-day mortality, nor was any interaction noted between either of these variables and diabetes (p = 0.6 and p = 0.9 for elective and rescue angioplasty, respectively).

Discussion

To our knowledge the present data demonstrate for the first time, and in the largest angiographic trial of thrombolytic

Figure 1. Kaplan-Meyer analysis of the effect of diabetes on 30-day survival after myocardial infarction. **Upper** and **lower curves** represent patients without (NDM) and with diabetes (DM), respectively.



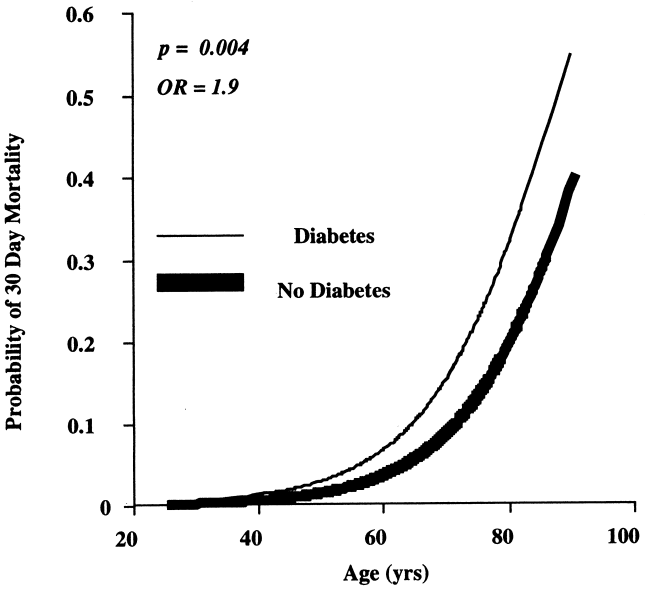


Figure 2. Effect of diabetes on probability of 30-day mortality after adjustment for age; p value refers to significance of difference between patients with and without diabetes; OR = odds ratio for 30-day mortality (diabetes vs. no diabetes) after adjustment for age.

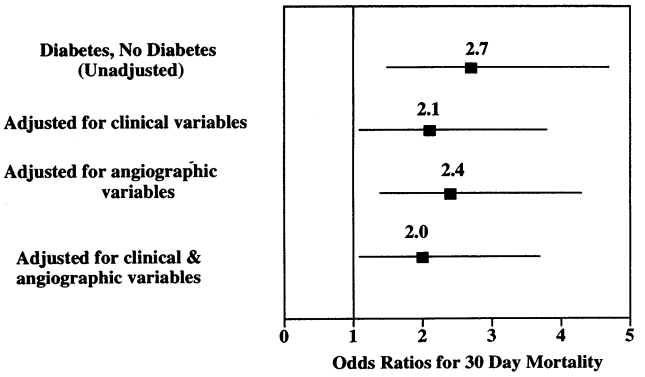


Figure 3. Effect of diabetes on 30-day mortality after adjustment for clinical or angiographic variables, or both. The relative odds ratios and 95% confidence interval (**horizontal lines**) for mortality are plotted for patients with diabetes versus without diabetes. A ratio >1.0 indicates greater risk for patients with diabetes. Clinical variables included age, gender, history of previous myocardial infarction, initial heart rate and blood pressure at time of entry into the trial. Angiographic variables included 90-min infarct-related artery TIMI flow grade and multivessel disease.

therapy in acute myocardial infarction to date, that diabetes is an independent determinant of early (30 day) mortality after myocardial infarction, even after adjustment for angiographic characterization.

Patency. Early infarct-related artery patency after thrombolytic therapy is a powerful determinant of early mortality in the setting of acute myocardial infarction (23). However, the relative efficacy of thrombolytic therapy in reestablishing infarct-related arterial flow in patients with diabetes, has been questioned. Patients with diabetes have elevated levels of circulating procoagulant factors and enhanced platelet aggregation (24–26). A decrease in endogenous thrombolysis potential has also been noted in patients with diabetes (24,27–31). However, our data did not demonstrate any significant difference in 90-min patency (TIMI flow grade 3) in response to thrombolytic therapy between patients with and without diabetes.

Reocclusion of initially patent infarct-related arteries was almost twofold greater in patients with than without diabetes. The failure of this difference to reach statistical significance may be the result of the relatively small sample size and limited power (23%) to detect a difference of this magnitude. Also of note is the extremely small total number of infarct-related artery reocclusions in this trial. This small number of events precludes any attempt at determining the independent determinants of reocclusion. On the basis of our data, we are unable to dismiss reocclusion of initially patent infarct-related arteries as a possible contributing factor to the excess mortality noted in patients with diabetes.

Degree of atherosclerosis. Patients with diabetes have been shown (15,32) to have more extensive and severe coronary atherosclerosis. Our data are in agreement, with 54.3% of diabetic patients with having multivessel coronary artery disease compared with only 40.5% of nondiabetic patients. However, this difference in the magnitude of underlying coronary disease does not account for the excess early (30 day) mortality noted in patients with diabetes as demonstrated by multivariable analysis. Of particular note, in a large cohort, we documented that patients with diabetes have a significantly narrower "normal" reference segment than nondiabetic patients, suggesting more extensive, nonangiographically identifiable epicardial coronary artery disease.

Ventricular function. We showed that severity of regional wall motion dysfunction, as defined by SD/chord, and extent of regional dysfunction, as defined by number of chords, in the territory of the infarct-related artery do not differ between patients with and without diabetes. This observation was true at 90 min and at 5 to 7 days after thrombolytic therapy. This finding suggests that there is no significant difference in myocardial cellular response to ischemic injury and subsequent reperfusion in patients with diabetes. It is also notable that despite the finding that patients with diabetes were treated 30 min later, possibly due to atypical or altered perceptions of ischemia, left ventricular function was not more severely affected among these patients.

Our data do show that there is a significant blunting of the hyperkinetic response in the noninfarct zone of patients with diabetes relative to the nondiabetic cohort. This finding appears to be primarily due to the presence of a greater number of myocardial infarctions as well as multivessel coronary artery disease in the diabetic cohort. However, diabetes itself does appear to contribute to this phenomenon, although to a much lesser degree. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) investigators (15) reported a similar finding. A neuropathy affecting the sympathetic nervous sys-

tem has been described in diabetes (33) and may serve as a potential explanation for this phenomenon. Although this difference was not maintained at 1 week after infarction, the attenuated hyperkinetic response of the noninfarct zone in the immediate peri-infarction period may partially account for the greater mortality noted in patients with diabetes.

Congestive heart failure was more common in patients with diabetes despite an ejection fraction comparable to nondiabetic patients. Indeed, diastolic dysfunction (34–37) due to interstitial fibrosis and protein glycosylation (38,39) rather than systolic dysfunction appears to be the hallmark of "diabetic cardiomyopathy." Diastolic dysfunction in our diabetic cohort may be a possible explanation for the increased prevalence of heart failure in this group relative to the nondiabetic cohort despite a similar degree of systolic dysfunction.

Procedure outcomes. We noted a greater than threefold increase in mortality in patients with diabetes who subsequently underwent elective angioplasty within 1 week after myocardial infarction. The TIMI-II investigators (40) also noted an increased 8-week mortality rate of 14.8% in patients with diabetes who underwent angioplasty within 18 to 48 h after infarction compared with 3.8% in patients without diabetes. However, we were unable to demonstrate that elective angioplasty itself is an independent predictor of 30-day mortality after adjustment for clinical and angiographic variables, nor was any interaction noted between diabetes and elective angioplasty. These data therefore suggest that elective angioplasty does not contribute significantly to the excess mortality noted in patients with diabetes in our trial cohort. However, this conclusion must be tempered by our limited sample size. We would suggest, therefore, that elective angioplasty in the week after myocardial infarction be limited in patients with diabetes to those with recurrent or inducible ischemia.

Patients with diabetes who underwent attempted rescue angioplasty also had a higher 30-day mortality rate than nondiabetic patients. The success rate of attempted rescue angioplasty tended to be lower in patients with diabetes, although the difference was of marginal statistical significance ($p = 0.052$). However, as with elective angioplasty, rescue angioplasty was not an independent determinant of 30-day mortality, nor was any significant interaction noted with diabetes. Again, the interpretation of our results is limited by our sample size and relative paucity of deaths.

Adjunctive medical therapy. There were significant differences between patients with and without diabetes with regard to adjunctive medical therapy during the hospital period and at the time of hospital discharge. A greater proportion of patients with diabetes received calcium channel blockers and ACE inhibitors than those without diabetes at each time period. The use of ACE inhibitors has been associated with increased survival after acute myocardial infarction (41). It is therefore unlikely that the greater use of ACE inhibitors in patients with diabetes in this study contributed to the excess mortality noted in this cohort. The greater use of calcium channel blockers in patients with than without diabetes may reflect the finding that a greater proportion of patients with diabetes in this study had a history of hypertension. Alternatively, the increased proportion of patients with diabetes receiving ACE inhibitors and calcium channel blockers in this study may simply reflect a chance occurrence due to the relatively small sample size. The effect of calcium channel blockers on mortality in the diabetic and nondiabetic cohorts could not be adequately evaluated because of the small sample size.

Mortality. The present data strongly support the numerous studies (6,42–46) that have demonstrated increased mortality in patients with diabetes in the setting of acute myocardial infarction. The excess mortality noted in patients with diabetes has been attributed to larger infarct size and more frequent pump failure (10,41,42) as well as a greater number of comorbid conditions (10,13,44). We performed a multivariable analysis to determine the independent prognostic importance of diabetes with regard to early (30 day) mortality after adjustment for other clinical and angiographic variables. Our data demonstrate that diabetes is an independent determinant of early mortality after adjustment for clinical variables. This finding is in agreement with the results previously reported by Lee et al. (22) in an analysis of the entire GUSTO-I population of 41,021 patients. With the addition of angiographic variables (90-min TIMI flow grade and number of diseased vessels) to the analysis, diabetes remained an independent determinant of early mortality. These results suggest that the excess mortality noted in patients with diabetes in the setting of acute myocardial infarction cannot be explained by differences in early patency in response to thrombolytic therapy, increased injury in response to ischemia and reperfusion, comorbid clinical conditions or the physiologic consequences of diabetes (i.e., greater extent of coronary artery disease and greater prevalence of previous myocardial infarctions). Our data suggest that other variables, as yet inadequately defined or unrecognized, account for the increased mortality noted in diabetic patients after acute myocardial infarction.

Study limitations. The present study has several limitations inherent to subgroup analysis. We examined the secondary hypothesis that diabetes affects regional left ventricular function in response to ischemia and reperfusion. We used the GUSTO-I Angiographic Trial data base, which was designed to evaluate the efficacy of several thrombolytic regimens on early patency and left ventricular function. Randomization did not control for diabetic status; thus, the size of the diabetic and nondiabetic patient groups differed greatly. The failure to detect differences in left ventricular function between diabetic and nondiabetic patients could be influenced by the availability of only 310 diabetic patients for analysis. However, we provided power calculations for all determinants of differences in regional and global ventricular function, which suggests that large differences were unlikely to have gone undetected. Furthermore, the adjustment process by means of multivariable logistic modeling cannot take into account small differences in baseline variables that may have a cumulatively important effect.

Other limitations include the fact that not all patients

underwent repeat catheterization at 5 to 7 days after infarction, although there was no difference in follow-up angiography rates between patients with and without diabetes. Also, because it was not a requirement of the study to have all rescue or elective angioplasty films reviewed in the core angiographic laboratory, a potential for bias exists for those particular analyses.

Conclusions. Our data demonstrate that diabetes is an independent determinant of early mortality after acute myocardial infarction in patients treated with thrombolytic therapy after adjustment for both clinical and angiographic variables. Thrombolytic therapy is equally efficacious in restoring early infarct-related artery patency in patients with and without diabetes. Reocclusion of initially patent infarct-related arteries may be more common in patients with diabetes and may contribute to early mortality. There is no significant difference in the regional ventricular response to injury/reperfusion in diabetic patients compared with nondiabetic patients. However, patients with diabetes exhibit a significantly blunted hyperkinetic response in the noninfarct zone immediately after ischemic injury. This phenomenon may contribute to the increased prevalence of congestive heart failure seen in patients with diabetes and possibly to mortality as well. patients with diabetes undergoing elective angioplasty after myocardial infarction may be at risk for adverse outcome, although the contribution of this procedure to the excess early mortality seen in patients with diabetes, if any, remains to be determined.

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