Journal of the American College of Cardiology Vol. 45, No. 4, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.10.054

Impact of Diabetes Mellitus on Myocardial Perfusion After Primary Angioplasty in Patients With Acute Myocardial Infarction

Abhiram Prasad, MD, MRCP, FACC,* Gregg W. Stone, MD, FACC,† Thomas D. Stuckey, MD, FACC,‡ Costantino O. Costantini, MD,† Peter J. Zimetbaum, MD, FACC,§ Michael McLaughlin, MD,§ Roxana Mehran, MD, FACC,† Eulogio Garcia, MD,‖ James E. Tcheng, MD, FACC,¶ David A. Cox, MD, FACC,# Cindy L. Grines, MD, FACC,** Alexandra J. Lansky, MD, FACC,† Bernard J. Gersh, MBChB, DPhil, FACC*

Rochester, Minnesota; New York, New York; Greensboro, Durham, and Charlotte, North Carolina; Boston, Massachusetts; Madrid, Spain; and Royal Oak, Michigan

OBJECTIVES We investigated the impact of diabetes mellitus on myocardial perfusion after primary percutaneous coronary intervention (PCI) utilizing myocardial blush grade (MBG) and ST-segment elevation resolution (STR).

BACKGROUND Diabetes is an independent predictor of outcomes after primary PCI for acute myocardial infarction (AMI). Whether the poor prognosis is due to lower rates of myocardial reperfusion is unknown.

METHODS Reperfusion success in those with and without diabetes mellitus was determined by measuring MBG (n = 1,301) and STR analysis (n = 700) in two substudies of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial among patients undergoing primary PCI for AMI.

RESULTS There were no differences between those with or without diabetes with regard to postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 (>95%), distribution of infarct-related artery, and the frequency of stent deployment or abciximab administration. Patients with diabetes mellitus were more likely to have absent myocardial perfusion (MBG 0/1, 56.0% vs. 47.1%, p = 0.01) and absent STR (20.3% vs. 8.1%, p = 0.002). Diabetes mellitus (hazard ratio [HR] 1.63 [95% confidence interval (CI) 1.17 to 2.28], p = 0.004) was an independent predictor of absent myocardial perfusion (MBG 0/1) and absent STR (HR 2.94 [95% CI 1.64 to 5.37], p = 0.005) by multivariate modeling.

CONCLUSIONS Despite similar high rates of TIMI flow grade 3 after primary PCI in patients with and without diabetes, patients with diabetes are more likely to have abnormal myocardial perfusion as assessed by both incomplete STR and reduced MBG. Diminished microvascular perfusion in diabetics after primary PCI may contribute to adverse outcomes. (J Am Coll Cardiol 2005;45:508–14) © 2005 by the American College of Cardiology Foundation

The major cause of morbidity and mortality in patients with diabetes mellitus is cardiovascular disease (1,2). The presence of diabetes is an independent predictor of early and late mortality after acute myocardial infarction (AMI) (2,3). The higher mortality in AMI patients with versus without diabetes may, in part, be due to more extensive coronary atherosclerosis and concomitant comorbid conditions, reduced cardiac reserve, and excessive delay from symptom onset to presentation (4–6). Treatment of diabetes with sulfonylurea oral hypoglycemic drugs may further diminish the ability of the myocardium to tolerate ischemia (7). Diabetes has also been associated with abnormal coronary endothelial function, diminished coronary flow reserve, and impaired ischemic preconditioning (8–10), all of which may result in abnormal myocardial perfusion.

Recent small studies suggest that acute outcomes in diabetic patients with AMI may be better after reperfusion with primary percutaneous coronary intervention (PCI) than thrombolytic therapy (5,11). However, compared with patients without diabetes, diabetics remain at increased risk for adverse outcomes after primary PCI. Whether this is, in part, due to abnormal myocardial perfusion after PCI in patients with diabetes has not been formally studied. We, therefore, examined the impact of diabetes mellitus on

From the *Division of Cardiovascular Diseases and Department of Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota; †Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; ‡Moses Cone Heart and Vascular Center, Greensboro, North Carolina; §Beth Israel Deaconess Medical Center, Boston, Massachusetts; ‖Hospital Gregorio Maranon, Madrid, Spain; ¶Duke Clinical Research Institute, Durham, North Carolina; #Mid Carolina Cardiology, Charlotte, North Carolina; and **William Beaumont Hospital, Royal Oak, Michigan. Drs. Lansky and Zimetbaum direct the two core laboratories utilized in the analysis. Dr. Stephen G. Ellis acted as guest editor for this paper.

Manuscript received September 7, 2004; revised manuscript received October 18, 2004, accepted October 26, 2004.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
CADILLAC	= Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial
CI	= confidence interval
HR	= hazard ratio
MACE	= major adverse cardiac events
MBG	= myocardial blush grade
OR	= odds ratio
PCI	= percutaneous coronary intervention
STR	= ST-segment resolution

myocardial reperfusion from a large multicenter, prospective study of primary PCI in AMI, utilizing two well-validated measures of myocardial perfusion and reperfusion success, resolution of ST-segment elevation (STR) (12–16) and the myocardial blush grade (MBG) (17–20).

METHODS

The details of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial protocol have been published previously (21). In brief, 2,082 patients of any age with AMI within 12 h of symptom onset undergoing primary PCI were enrolled in 76 centers in nine countries between November 1997 and September 1999, and randomized in a 2 × 2 factorial design to primary balloon angioplasty versus stenting, with or without abciximab. The principal exclusion criteria consisted of cardiogenic shock, saphenous vein graft occlusion, and lesions otherwise not amenable to stent implantation. Clinical follow-up continued for one year.

An independent committee blinded to randomization adjudicated all primary end point events. Major adverse cardiac events (MACE) were defined as a composite of death, reinfarction, ischemic-driven target vessel revascularization, or disabling stroke as previously defined (21). Diabetic status was classified by treatment with diet alone, oral hypoglycemic agents, and insulin. The principal clinical results of the CADILLAC trial stratified by diabetes have been previously reported (22). The present analyses are restricted to the impact of diabetes on myocardial perfusion as assessed in formal STR and MBG substudies within the CADILLAC trial.

MBG substudy. Myocardial blush grade is an angiographic surrogate of myocardial perfusion after PCI, and strongly correlates with survival after reperfusion therapy in AMI (17–20). The details of the CADILLAC myocardial blush substudy have been previously published (23). In brief, myocardial blush in the distribution of the infarct vessel after PCI was analyzed using the methodology of van't Hof et al. (17) at an independent angiographic core laboratory at the Cardiovascular Research Foundation in New York City blinded to clinical outcomes. Based on the maximal densitometric degree of contrast opacification, MBG in 1,301 patients was scored as MBG 0/1 = no or minimal myocardial contrast opacification; MBG 2 = moderate contrast opacification but less than in either an ipsilateral or contralateral noninfarct artery; and MBG 3, normal myocardial blush or contrast opacification, comparable with the other coronary arteries. When myocardial blush persisted ("staining"), MBG-0 was assigned.

STR substudy. ST-segment monitoring is a well-validated, noninvasive method for assessing the efficacy of myocardial reperfusion therapy in patients with AMI (12–15), and STR has been correlated with the restoration of epicardial and microvascular blood flow and myocyte function (16). The methodology of the CADILLAC STR substudy has also previously been reported (24). In brief, 700 patients who met the following criteria were entered into a formal substudy to examine the impact of electrocardiographic STR after AMI: 1) paired electrocardiograms (ECG) at baseline and within 4 h after PCI (mean 1.8 ± 0.8 h) with >1 mm baseline ST-segment elevation in two contiguous leads in the infarct territory; and 2) absence of conditions on both ECGs confounding interpretation, including left bundle branch block, pacing, preexcitation, ectopy, missing leads, and artifact. ST-segment resolution was measured at an independent core electrocardiographic laboratory (Beth Israel Deaconess Medical Center, Boston, Massachusetts) blinded to clinical outcomes. ST-deviation was measured with digital calipers to the nearest 0.01 mV. The summed level of ST-segment elevation was calculated for anterior myocardial infarction in V_1 to V_6, I, and aVL, and for inferior myocardial infarction in leads II, III, aVF, V_5, and V_6. As per Schroder et al. (12), STR was classified as complete (>70%), partial (30% to 70%), or absent (<30%).

Statistical analysis. Categorical variables were compared with Fisher exact test for paired comparisons and the chi-square test for trend for three-way comparisons. Continuous variables are presented as medians and interquartile ranges, and were compared using the Kruskal-Wallis nonparametric test. Adverse event rates during follow-up were summarized and displayed as Kaplan-Meier estimates and compared using the log-rank test. Stepwise logistic regression analysis was used to identify independent predictors of absent STR (<30%) and absent or minimal blush (MBG 0/1) after PCI. Baseline clinical, angiographic, and procedural variables as seen in Tables 1 and 2 were included in the multivariate models with an entry and exit criteria of $p < 0.10$. Cox proportional hazard regression was used to identify independent correlates of mortality in diabetics.

RESULTS

Baseline characteristics. There were 232 (17.8%) diabetics among the 1,301 patients who were enrolled in the formal MBG substudy, and 118 (16.8%) diabetics among the 700 patients enrolled in the formal STR substudy. The clinical characteristics of patients with and without diabetes for the two substudies are summarized in Table 1. Patients with

Table 1. Baseline Characteristics Stratified by Diabetic Status

	MBG Substudy		STR Substudy	
	No Diabetes	Diabetes	No Diabetes	Diabetes
Number	1,069	232	582	118
Age, yrs	60 (50, 69)	62 (55, 70)†	59 (49, 68)	62 (55, 70)†
Male, %	74.5	59.9‡	75.1	66.1
Hypertension, %	44.1	66.4‡	44.8	58.5†
Hypercholesterolemia, %	37.8	44.4	36.8	34.7
Current smoker, %	46.8	31.0‡	46.4	38.1
Peripheral vascular disease, %	2.4	3.0	1.9	6.8†
Creatinine clearance <60 cc/min, %	18.9	22.5	17.0	22.6
Prior myocardial infarction, %	13.4	17.2	11.3	14.4
Prior coronary angioplasty, %	11.0	12.0	9.3	8.5
Prior bypass surgery, %	1.9	4.3*	1.2	1.7
Killip class 2/3, %	8.9	16.0†	8.5	11.9
Symptoms to hospital arrival, h	1.8 (1.0, 3.6)	2.1 (1.2, 4.4)*	1.5 (1.0, 2.8)	2.0 (1.1, 3.2)*
Symptoms to angioplasty, h	4.0 (2.9, 6.2)	4.9 (3.3, 7.4)‡	3.4 (2.7, 5.0)	4.0 (2.9, 5.6)*
Insulin therapy, %	—	22.4	—	14.4

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$.
MBG = myocardial blush grade; STR = ST-segment resolution.

diabetes were older, more likely to be female and have hypertension and congestive heart failure at presentation, and presented later from the symptom onset, but were less likely to be current smokers. The differences in baseline characteristics are consistent with the diabetic status of the patients and have been observed in previous studies (5); however, we cannot exclude selection bias resulting from a subgroup analysis. As seen in Table 2, diabetic patients were more likely to have multivessel coronary artery disease and preprocedure Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 than nondiabetic patients. There were no differences in the distribution of the infarct-related artery, reference vessel diameter, severity of stenosis, rates of stent implantation or abciximab administration, or postprocedural TIMI flow grade 3 between diabetic and nondiabetic patients.

MBG and STR after PCI in diabetes. There was no difference in the prevalence of diabetes among the patients who were and those who were not included in the MBG and STR subanalyses in the CADILLAC trial (23,24). As seen in Figure 1, absent myocardial perfusion (MBG 0/1)

Table 2. Angiographic and Procedural Data Stratified by Diabetic Status

	MBG Substudy		STR Substudy	
	No Diabetes	Diabetes	No Diabetes	Diabetes
Baseline ejection fraction, %	50 (40, 56)	50 (40, 60)	48 (40, 55)	47 (35, 55)
Number of diseased vessels, %				
One	53.4	40.9‡	56.4	40.7†
Two	32.0	37.5	31.3	37.3
Three	14.6	21.6*	12.4	22.0†
Infarct vessel, %				
Left anterior descending	35.6	33.6	43.6	39.0
Right coronary artery	45.8	50.9	43.6	51.7
Circumflex artery	18.1	15.5	12.5	9.3
TIMI flow (% of patients)				
Preprocedure				
Grade 0/1	70.8	57.1‡	74.7	60.3†
Grade 2	9.6	10.4	10.2	14.7
Grade 3	19.6	32.5‡	15.1	25.0*
Postprocedure				
Grade 0/1	1.1	1.7	1.2	1.7
Grade 2	2.5	2.6	2.8	2.6
Grade 3	96.3	95.7	96.0	95.7
Reference diameter (mm)	2.95 (2.61, 3.33)	2.86 (2.59, 3.25)	2.97 (2.62, 3.41)	2.96 (2.62, 3.30)
Diameter stenosis (%)				
Preprocedure	100 (77.3, 100)	100 (69.2, 100)	100 (79.6, 100)	100 (73.0, 100)
Postprocedure	17.9 (9.1, 26.9)	17.5 (8.9, 25.2)	18.2 (8.5, 27.7)	17.4 (10.1, 24.9)
Stent implantation, %	56.3	57.3	56.5	56.8
Abciximab administered, %	51.6	56.5	50.9	50.0

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

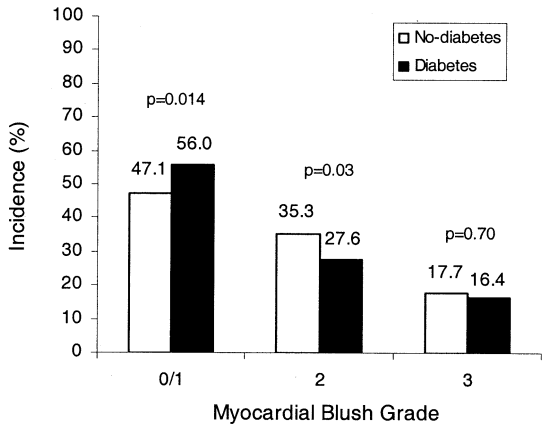

Figure 1. Myocardial perfusion grade after intervention in patients with and without diabetes.

after primary PCI was significantly more common in diabetic compared with nondiabetic patients. By multivariate analysis, diabetes (odds ratio [OR] 1.63 [95% confidence interval (CI) 1.17 to 2.28], p = 0.004), anterior infarction (OR 4.14 [95% CI 3.18 to 5.4], p < 0.0001), and prolonged time from symptom onset to angioplasty (OR 1.07 [95% CI 1.03 to 1.11], p = 0.0008) were independent predictors of absent postprocedural myocardial perfusion.

Absent STR was also significantly more frequent in patients with compared to those without diabetes (Fig. 2). By multivariate analysis, diabetes (OR 2.94 [95% CI 1.60 to 5.37], p = 0.0005), anterior infarction (OR 3.98 [95% CI 2.21 to 7.17], p < 0.0001), and prolonged time from symptom onset to angioplasty (OR 1.11 [95% CI 1.04 to 1.19], p = 0.002) were independent predictors of absent STR.

Clinical implications of myocardial perfusion after primary PCI in patients with diabetes. There was an inverse relationship between MBG and mortality in diabetic patients, both at 30 days and 1 year, though this relationship was not statistically significant (Fig. 3). By multivariate analysis, lower creatinine clearance (hazard ratio [HR] 1.06 [95% CI 1.03 to 1.11], p = 0.0003) was the only independent predictor of 30-day mortality in patients with diabetes in this substudy. Absent MBG was not significantly predictive of mortality when forced into this model (HR 1.67 [95% CI 0.33 to 8.44], p = 0.54). Reduced creatinine clearance (HR 1.03 [95% CI 1.01 to 1.04], p = 0.008) and admission Killip class 2/3 (HR 3.63 [95% CI 1.27 to 10.42], p = 0.02) were independent predictors of one-year mortality. In this model the MBG HR for one-year mortality was 3.05 (95% CI 0.86 to 10.84, p = 0.08).

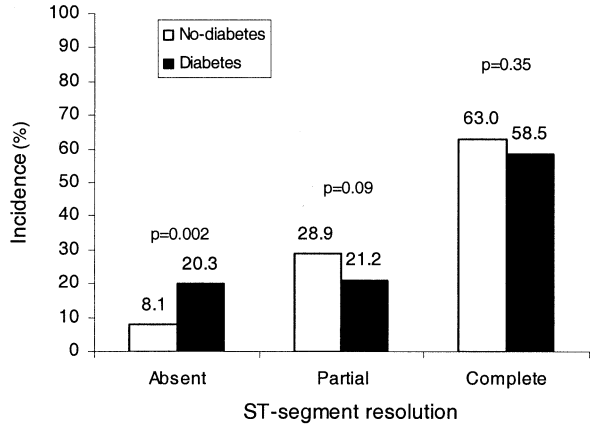

Figure 2. ST-segment resolution after intervention in patients with and without diabetes.

As seen in Figure 4, absent STR was a statistically significant univariate predictor of mortality in diabetic patients. By multivariate analysis in this substudy, lower creatinine clearance (HR 1.16 [95% CI 1.03 to 1.29], p = 0.01) was the only independent predictor of 30-day mortality in diabetics. Absent STR was weakly predictive of 30-day mortality when forced into this model (HR 11.04 [0.70 to 165.60], p = 0.08). However, absent STR was a statistically significant independent predictor of one-year mortality in diabetic patients (HR 11.71 [95% CI 1.53 to 89.90], p = 0.02), as was reduced creatinine clearance (HR 1.09 [95% CI 1.03 to 1.14], p = 0.02) and the presence of triple-vessel disease (HR 9.90 [95% CI 1.31 to 75.05], p = 0.03).

DISCUSSION

The major findings of the present study are: 1) despite similar rates of TIMI flow grade 3 after primary PCI in patients with and without diabetes, patients with diabetes are more likely to have abnormal myocardial perfusion as assessed by both incomplete STR and reduced MBG; and 2) diminished microvascular perfusion in diabetics after primary PCI may contribute to the increased mortality rates in these patients.

Despite the effective restoration of normal epicardial flow rates in >95% of patients with diabetes in this study, complete resolution of ST-segment elevation was observed in only approximately half of the patients. Similarly, only approximately half of patients had normal myocardial perfusion as assessed angiographically by the MBG. By multivariate analysis, the presence of diabetes (as well as anterior AMI and delayed reperfusion) was an independent predictor of both absent STR and a closed microvasculature.

Few prior reports have examined myocardial perfusion in diabetic patients after reperfusion therapy. In a previous study examining pooled data from four TIMI trials, complete STR at 90 min tended to be less often present in patients with diabetes, but only in those without TIMI flow grade 3 (25). A lower likelihood of early STR, defined as ≥50% decrease in ST-segment elevation at 30 min, has been reported from a small study in insulin-requiring diabetics after primary PCI (26). The results of the present multicenter study thus confirm and extend the findings from these studies in demonstrating impaired myocardial perfusion in a relatively large diabetic cohort after primary PCI, independent of epicardial flow rates.

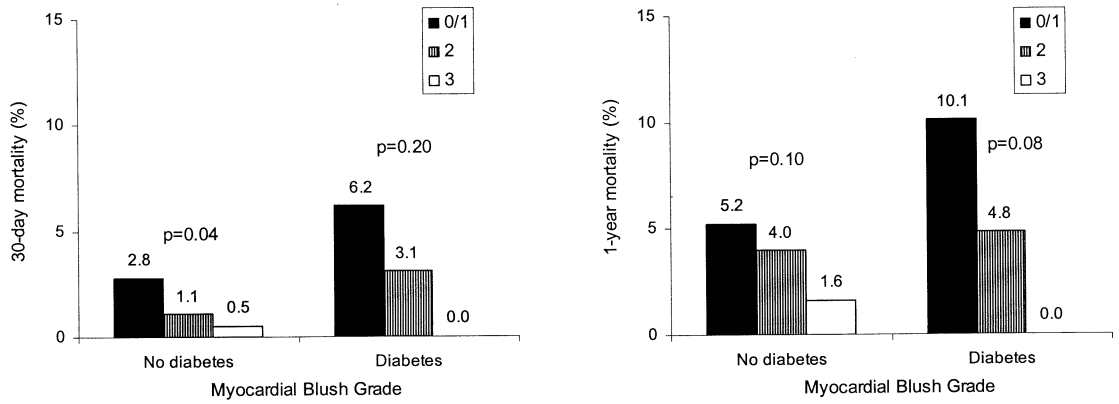

Figure 3. Relationship between myocardial blush grade and 30-day **(left)** and 1-year **(right)** mortality in patients with (n = 232) and without diabetes (n = 1,069).

Persistent ST-segment elevation and abnormal myocardial blush in the presence of normal epicardial blood flow are indicative of diminished microvascular blood flow and impaired tissue perfusion, often referred to as the "no-reflow phenomenon" (27,28). Thus, our findings confirm that myocardial microvascular flow is more frequently impaired in diabetes. Impaired myocardial reperfusion as evidenced by diminished STR and abnormal MBG after reperfusion therapy is a powerful predictor of decreased left ventricular functional recovery and greater infarct size (27,29,30), as well as short- and long-term mortality (12,13,15,20,23,24). Thus, abnormal myocardial perfusion may, in part, explain the poor prognosis in patients with, compared to those without, diabetes after primary PCI (31). Our study also confirms the utility of electrocardiographic STR and MBG in predicting mortality in diabetic patients treated with PCI. A negative stepwise relationship between the magnitude of STR and MBG, and 30-day and 1-year mortality was found. In the current study, STR was more useful than MBG in predicting long-term outcomes in diabetics. However, given the fact that the present report was based on different groups of patients in two separate substudies, additional large-scale studies are required to examine the relative prognostic utility of STR and MBG.

While the precise pathophysiologic mechanisms by which diabetes contributes to microvascular injury remain unknown, several potential explanations have been postulated. First, diabetes is associated with a prothrombotic and inflammatory state; microthrombi and leucocyte accumulation in the capillaries of diabetic patients may, thus, lead to coronary microvascular obstruction (32,33). Second, coronary endothelial and smooth muscle dysfunction due to oxidative stress accompanied by reduced nitric oxide bioavailability and increased endothelin release may lead to microvascular spasm and reduce myocardial perfusion after PCI in diabetic patients (33). Third, the acute recruitment of coronary collaterals appears to be impaired in diabetic compared with nondiabetic patients (34). These observations require validation, and further studies are needed to elucidate the mechanisms of microvascular hypoperfusion in diabetics with the aim of developing new therapies.

Study limitations. The current analyses, as post-hoc analyses of two substudies, are subject to both recognized and unknown biases; STR and MBG were the only markers of

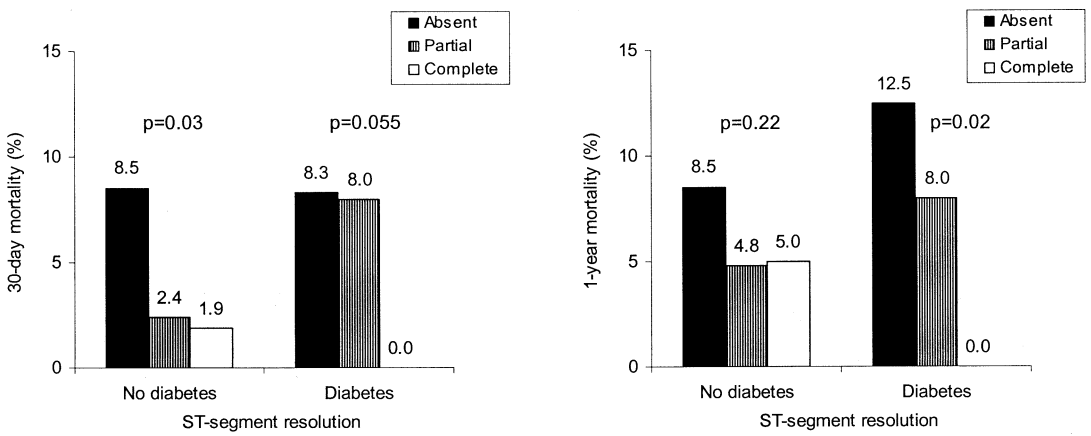

Figure 4. Relationship between the ST-segment resolution and 30-day **(left)** and 1-year **(right)** mortality in patients with (n = 118) and without diabetes (n = 582).

myocardial perfusion examined in the present study. Other imaging modalities of microcirculatory function such as contrast echocardiography, positron emission tomographic scanning, and invasive measures of coronary flow reserve (Doppler) may provide additional insights regarding microcirculatory function in the diabetic patient with AMI after reperfusion. An interaction between insulin therapy and myocardial perfusion could not be determined due to the relatively small number of insulin-treated patients included in the analyses. The use of coronary stent has increased significantly since this study was conducted, which may limit the applicability of our findings to current practice. However, recent data suggests that stent deployment does not alter myocardial perfusion (23,24). The present study examined the impact of myocardial perfusion on mortality only; the impact of diabetes and microcirculatory function on myocardial salvage and recovery of left ventricular function was not studied. Finally, while CADILLAC is the largest multicenter trial of primary PCI to date, significantly larger, specifically designed studies are required to comprehensively evaluate all the variables responsible for the adverse prognosis in diabetic patients with AMI.

Conclusions and clinical implications. With contemporary interventional approaches, the procedural success rate of primary PCI in diabetics with AMI is equivalent to nondiabetic patients. However, a greater proportion of diabetic than nondiabetic patients fail to achieve normal myocardial perfusion, a finding associated with higher mortality in this patient cohort. Additional research is required to develop novel device-based and pharmacologic approaches to enhance microcirculatory function after primary PCI, which may improve the prognosis of patients with diabetes and AMI. In this regard, assessment of STR and MBG after reperfusion are relatively simple, noninvasive methods with prognostic utility beyond TIMI flow grade 3, and, as such, should be included in future studies of reperfusion.

Reprint requests and correspondence: Dr. Gregg W. Stone, The Cardiovascular Research Foundation, Columbia University Medical Center, Herbert Irving Pavilion, 5th Floor, 161 Fort Washington Avenue, New York, New York 10032. E-mail: gstone@crf.org.

REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979;59:8–13.
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
3. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1997;30:171–9.
4. Laskey WK, Selzer F, Vlachos HA, et al. Comparison of in-hospital and one-year outcomes in patients with and without diabetes mellitus undergoing percutaneous catheter intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol 2002;90:1062–7.
5. Hasdai D Granger CB, Srivatsa SS, et al. Diabetes mellitus and outcome after primary coronary angioplasty for acute myocardial infarction: lessons from the GUSTO-IIb Angioplasty substudy. Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes. J Am Coll Cardiol 2000;35:1502–12.
6. Moreno R, Zamorano J, Almeria C, et al. Diabetes leads to less contractile reserve after myocardial infarction (abstr). Eur Heart J 2002;4 Suppl:316.
7. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR, Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 1999;33:119–24.
8. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecar E, Attali J-R. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. Diabetes 1993; 42:1017–25.
9. Nahser PJ, Jr., Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation 1995;91:635–40.
10. Ishihara M, Inoue I, Kawagoe T, et al. Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. J Am Coll Cardiol 2001;38:1007–11.
11. Hsu LF, Mak KH, Lau KW, et al. Clinical outcomes of patients with diabetes mellitus and acute myocardial infarction treated with primary angioplasty or fibrinolysis. Heart 2002;88:260–5.
12. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST-segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994;24:384–91.
13. Schroder R, Wegscheider K, Schroder K, et al., for the INJECT Trial Group. Extent of early ST-segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol 1995;26:1657–64.
14. Santoro GM, Antoniucci D, Valenti R, et al. Rapid reduction of ST-segment elevation after successful direct angioplasty in acute myocardial infarction. Am J Cardiol 1997;80:685–9.
15. Gibson CM, Cannon CP, Murphy SA, et al. The relationship of the TIMI myocardial perfusion grade to mortality after thrombolytic administration. Circulation 2000;101:125–30.
16. de Lemos JA, Antman EM, McCabe CH, et al. ST-segment resolution and infarct related artery patency and flow after thrombolytic therapy. Am J Cardiol 2000;85:299–304.
17. van't Hof AW, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302–6.
18. Stone GW, Peterson MA, Lansky AJ, et al. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am Coll Cardiol 2002;39:591–7.
19. Henriques JP, Zijlstra F, van't Hof AW, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 2003;107:2115–9.
20. Haager PK, Christott P, Heussen N, et al. Prediction of clinical outcome after mechanical revascularization in acute myocardial infarction by markers of myocardial reperfusion. J Am Coll Cardiol 2003;41:532–8.
21. Stone GW, Grines CL, Cox DA, et al., The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–66.
22. Stuckey TD, Stone GW, Cox DA, et al. Impact of stenting and glycoprotein IIb/IIIa receptor blockade in patients with diabetes mellitus undergoing primary angioplasty in acute myocardial infarction: the CADILLAC trial. Am J Cardiol 2005. In Press.
23. Costantini CO, Stone GW, Mehran R, et al. Frequency, correlates and clinical implications of myocardial perfusion after primary angio-

plasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. J Am Coll Cardiol 2004;44:305–12.
24. McLaughlin MG, Stone GW, Aymong E, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the CADILLAC trial. J Am Coll Cardiol 2004;44:1215–23.
25. Angeja BG, de Lemos J, Murphy SA, et al. Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. Am Heart J 2002;144:649–56.
26. Antoniucci D, Valenti R, Migliorini A, et al. Impact of insulin-requiring diabetes mellitus on effectiveness of reperfusion and outcome of patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 2004;93:1170–2.
27. Feldman LJ, Coste P, Furber A, et al., Optimal STenting-2 Investigators. Incomplete resolution of ST-segment elevation is a marker of transient microcirculatory dysfunction after stenting for acute myocardial infarction. Circulation 2003;107:2684–9.
28. Hoffmann R, Haager P, Lepper W, Franke A, Hanrath P. Relation of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction. Heart 2003;89:1147–51.
29. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty. Circulation 2002;106:313–8.
30. Dong J, Ndrepepa G, Schmitt C, et al. Early resolution of ST-segment elevation correlates with myocardial salvage assessed by Tc-99m sestamibi scintigraphy in patients with acute myocardial infarction after mechanical or thrombolytic reperfusion therapy. Circulation 2002;105:2946–9.
31. Harjai KJ, Stone GW, Boura J, et al. Comparison of outcomes of diabetic and nondiabetic patients undergoing primary angioplasty for acute myocardial infarction. Am J Cardiol 2003;91:1041–5.
32. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. J Am Coll Cardiol 2003;41:1071–7.
33. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy. Circulation 2003;108:1527–32.
34. Werner GS, Richartz BM, Heinke S, Ferrari M, Figulla HR. Impaired acute collateral recruitment as a possible mechanism for increased cardiac adverse events in patients with diabetes mellitus. Eur Heart J 2003;24:1134–42.